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207 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides, polypeptides
5 encoded by these polynucleotides, antibodies that bind these polypeptides, uses of
such polynucleotides, polypeptides, and antibodies, and their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a
10 membrane, human cells and other eucaryotes are subdivided by membranes into many
functionally distinct compartments. Each membrane-bounded compartment, or
organelle, contains different proteins essential for the function of the organelle. The
cell uses "sorting signals," which are amino acid motifs located within the protein, to
target proteins to particular cellular organelles.

15 One type of sorting signal, called a signal sequence, a signal peptide, or a
leader sequence, directs a class of proteins to an organelle called the endoplasmic
reticulum (ER). The ER separates the membrane-bounded proteins from all other
types of proteins. Once localized to the ER, both groups of proteins can be further
directed to another organelle called the Golgi apparatus. Here, the Golgi distributes
20 the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes,
and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the
extracellular space as a secreted protein. For example, vesicles containing secreted
proteins can fuse with the cell membrane and release their contents into the
25 extracellular space - a process called exocytosis. Exocytosis can occur constitutively
or after receipt of a triggering signal. In the latter case, the proteins are stored in
secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly,
proteins residing on the cell membrane can also be secreted into the extracellular
space by proteolytic cleavage of a "linker" holding the protein to the membrane.

30 Despite the great progress made in recent years, only a small number of genes
encoding human secreted proteins have been identified. These secreted proteins

include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical diseases, disorders, and/or conditions by using secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant and synthetic methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting diseases, disorders, and/or conditions related to the polypeptides and polynucleotides, and therapeutic methods for treating such diseases, disorders, and/or conditions. The invention further relates to screening methods for identifying binding partners of the polypeptides.

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA

preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5 kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig

analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard,
5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to
10 sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon
15 sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower
20 percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE,
25 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress
30 background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking

reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA⁺ sequences (such as any 3' terminal polyA⁺ tract of a cDNA shown in the sequence listing), or to a
5 complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotide of the present invention can be composed of any
10 polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA
15 that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for
20 example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide
25 isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications
30 can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in

a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or
5 may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of
10 covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.
15 (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)
20 "SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the
25 present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not
30 more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

5 This gene is expressed primarily in melanocytes and, to a lesser extent, in testes, ovary, kidney and other tissues.

 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of neural crest derived cells including pigmentation defects, melanoma, reproductive organ defects, and defects of the kidney . Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin, reproductive, and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. melanocytes, testes, ovary, kidney, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

 The tissue distribution in melanocytes indicates that the protein product of this gene is useful for treating disorders that arise from alterations in the number or fate of neural crest derived cells including cancers such as melanoma and defects of the developing reproductive system.

 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2512 of SEQ ID NO:11, b is an integer of 15 to 2526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

10 ENMICVKCLPQYPEHSKHV (SEQ ID NO:487). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed
15 by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in infant brain and fetal lung.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders of the brain or lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
25 the above tissues or cells, particularly of the central nervous and pulmonary systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, lung, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a
30 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in infant brain and fetal lung indicates that the protein product of this gene is useful for treating or diagnosing disorders associated with abnormal proliferation of cells in the Central nervous system and developing lung. Furthermore, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1117 of SEQ ID NO:12, b is an integer of 15 to 1131, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

ARVAFHLICRYILPTVYCHV (SEQ ID NO:488). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to

these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are
5 also encompassed by the invention.

This gene is expressed primarily in breast lymph node, and to a lesser extent, in ovarian cancer and chondrosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
10 and for diagnosis of diseases and conditions which include, but are not limited to, immune responses such as inflammation or immune surveillance for tumors. This gene may be important for inflammatory responses associated with tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell
15 type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lymph nodes, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such
20 a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 251 as residues: Lys-45 to Val-50, and/or Lys-69 to Arg-76.

The tissue distribution in breast lymph node indicates that the protein product
25 of this gene is useful for the treatment or diagnosis of immune responses, including those associated with tumor-induced inflammation. Furthermore, given the tissue distribution, the gene product may also be involved in lymphopoiesis. In a case such as this, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. Protein, as well as, antibodies directed against the protein
30 may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
5 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 927 of SEQ ID NO:13, b is an integer of 15 to 941, where both a and b correspond to the positions of nucleotide
10 residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
ELVESPGAAGNSARSGNVVC (SEQ ID NO:489). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
20 these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

25 This gene is expressed primarily in T-cells and T-cell lymphomas.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological diseases involving T-cells such as inflammation, autoimmunity, and
30 cancers including T-cell lymphomas. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

tissues or cells, particularly of T-cells and other cells of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or
5 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells and T-cell lymphomas indicates that the protein product of this gene is useful for diagnosing and treating T-cell based
10 disorders such as inflammatory diseases, autoimmune disease and tumors including T-cell lymphomas. Furthermore, the tissue distribution indicates that the polypeptides or polynucleotides are useful for the treatment, prophylaxis, and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. Additionally,
15 expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:14, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

This gene is expressed primarily in activated monocytes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, autoimmunity, infection, or disorders involving activation of monocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 253 as residues: Asp-19 to Arg-31.

The tissue distribution indicates that the protein product of this gene is useful for diagnosing or treating diseases that result in activation of monocytes including infections, inflammatory responses or autoimmune diseases. Furthermore, expression of this gene product in monocytes also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1004 of SEQ ID NO:15, b is an integer of 15 to 1018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

5 The translation product of this gene shares sequence homology with terminal deoxynucleotidyltransferase which is thought to be important in catalyzing the elongation of oligo- or polydeoxynucleotide chains.

 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

10 FKKLVNPRXQGIRHEEEAVSWQERR (SEQ ID NO:490). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are
15 encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

 This gene is expressed primarily in activated human neutrophils, and to a lesser extent in T-cells, primary dendritic cells and bone marrow cells.

20 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly those of the blood such as leukemia and deficiencies in neutrophils such as neutropenia, and immune system disorders. Similarly,
25 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune,
30 cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils and other immune cells, combined with the homology to terminal deoxynucleotidyltransferase indicates that the protein product of this gene is useful for the treatment and differential diagnosis of acute leukemias. Alternatively, this gene may function in the proliferation of neutrophils and be useful as a treatment for neutropenia, for example, following neutropenia as a result of chemotherapy. Additionally, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. This is particularly supported by the expression of this gene product in bone marrow, which is a primary site of definitive hematopoiesis. Expression of this gene product in T cells and primary dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 647 of SEQ ID NO:16, b is an integer of 15 to 661, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

The translation product of this gene exhibits a reasonable homology to the human chorionic gonadotropic (HCG) analogue-GT beta-subunit as disclosed in U.S.

Patent No. 5,508,261 and PCT Publication No. WO 92/22568. There is a high degree of conservation of the structurally important cysteine residues between these proteins.

This gene is expressed primarily in IL-1 and LPS induced neutrophils.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in
10 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid
15 and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment/diagnosis of diseases of the immune system, since
20 expression is primarily in neutrophils, and thus the translation product of this gene may be useful as a growth factor for the differentiation and/or proliferation of neutrophils for the treatment of neutropenia, for example following chemotherapy.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
25 related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
30 formula of a-b, where a is any integer between 1 to 539 of SEQ ID NO:17, b is an integer of 15 to 553, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

5 This gene is expressed primarily in IL-1 and LPS-induced neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies.

10 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and
15 wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
20 NO: 256 as residues: Ser-14 to Pro-22, and/or Leu-43 to Val-53.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment and diagnosis of diseases of the immune system, since expression is primarily in neutrophils, and thus the translation product of this gene may be useful as a growth factor for the differentiation and/or proliferation of
25 neutrophils for the treatment of neutropenia, for example following chemotherapy.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 855 of SEQ ID NO:18, b is an integer of 15 to 869, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

When tested against Jurkat cell lines, supernatants removed from cells expressing this gene activated the NF-kB transcription factor. Thus, it is likely that
10 the protein encoded by this gene activates Jurkat cells by activating a transcriptional factor found within these cells. Nuclear factor kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity.

15 This gene is expressed primarily in IL-1 and LPS induced neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies.
20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and
25 wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
30 NO: 257 as residues: Tyr-22 to His-35.

The tissue distribution in neutrophils, combined with the biological activity data suggest that the protein product of this gene is useful for the treatment and/or

diagnosis of diseases of the immune system, since expression is primarily in neutrophils, and thus the translation product of this gene may be useful as a growth factor for the differentiation and/or proliferation of neutrophils for the treatment of neutropenia, for example following chemotherapy.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 945 of SEQ ID NO:19, b is an integer of 15 to 959, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

20

This gene is expressed primarily in activated T-cells and to a lesser extent in endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
25 and for diagnosis of diseases and conditions which include, but are not limited to, immune dysfunctions including cancer of the T lymphocytes and autoimmune disorders and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above
30 tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph,

serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution in activated T-cells indicates that the protein product of this gene is useful for the treatment and/or diagnosis of immune disorders, particularly of T-cell origin, and may act as a growth factor for particular subsets of T-cells such as CD4 positive cells, which would make this a useful therapeutic for the treatment of HIV and other immune compromising illnesses. Furthermore, this gene
10 product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of AIDS or other immune compromising diseases (e.g. by boosting immune responses).

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
15 related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
20 formula of a-b, where a is any integer between 1 to 1432 of SEQ ID NO:20, b is an integer of 15 to 1446, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

25

The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in fetal tissues, such as liver/spleen and brain,
30 as well as in placental tissue.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for the diagnosis of many developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. fetal, placental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful as a growth factor or differentiation factor for particular cell types in the developing fetus and may be useful in replacement or other types of therapy in cases where the gene is expressed aberrantly. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1457 of SEQ ID NO:21, b is an integer of 15 to 1471, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

ISVLXYPHCVVHELPELTAESLEAGDSNQFCWRNLFSCINLLRILNKLTKWKH
SRTMMLVVFKSAPILKRALKVKQAMMQLYVLKLLKVQTKYLGRQWRKSN
MKTMSAIYQKVRHRLNDDWAYGNDLDARPWDFQAEECALRANIERFNARR
YDRAHSNPDFLPVDNCLQSVLGQRVDLPEDFQMNYDLWLEREVFSKPISWEE
LL (SEQ ID NO:491),
MRAASPPASASDLIEQQKGRGREHKALIKQDNLDAFNERD
PYKADDSREEEENDDDNSLEGETFPLERDEVMPPLQHPQTDRLXCPKGLP
WXPKVREKDIEMFLESSRSKFIGYTLGSDTNTVVGLPRPIHESI KTLKQHKYTS
IAEVQAQMEEYLRSPLSGGEEVEQVPAETLYQGLPSLPQYMIALLKILLA
AAPT SKAKTDSINILADVLP EEMPTTVLQSMKLGVDVNRHKEVTVKAISAVLL
LLKHFKLNHVYQFEYMAQHLVFANCIPLILKFFNQNIMSYITAKNSISVLDYP
HCVVHELPELTAESLEAGDSNQFCWRNLFSCINLLRILNKLTKWKHSRTMML
VVFKSAPILKRALKVKQAMMQLYVLKLLKVQTKYLGRQWRKSNMKTMSAI
YQKVRHRLNDDWAYGNDLDARPWDFQAEECALRANIERFNARRYDRAHSN
PDFLPVDNCLQSVLGQRVDLPEDFQMNYDLWLEREVFSKPISWEELLQ (SEQ
ID NO:492),
MRAASPPASASDLIEQQKGRGREHKALIKQDNLDAFNERDPYKADDSRE
(SEQ ID NO:493), EEEENDDDNSLEGETFPLERDEVMPPLQHPQTDRLX
CPKGLPWX (SEQ ID NO:494), PKVREKDIEMFLESSRSKFIGYTLGSDTNTV
VGLPRPIHESI KTLKQHKYT (SEQ ID NO:495), SIAEVQAQMEEYLRSPLSGG
EEVEQVPAETLYQGLPSLPQYMIA (SEQ ID NO:496), LLKILLAAAPT SKAK

TDSINILADVLPEEMPTTVLQSMKLGVDVNRHK (SEQ ID NO:497), EVIVKA
 ISAVLLLLLKHFKLNHVYQFEYMAQHLVFANCIPLILKFFNQNI (SEQ ID
 NO:498),
 MSYTTAKNSISVLDYPHCVVHELPELTAESLEAGDSNQFCWRNLFSCI (SEQ ID
 5 NO:499), NLLRLNKLTKWKHSRTMMLVVFKSAPILKRALKVKQ
 AMMQLYVLKL (SEQ ID NO:500),
 LKVQTKYLGRQWRKSNMKTMSAIYQKVRH RLNDDWAYGNLDLARP (SEQ
 ID NO:501), WDFQAEECALRANIERFNARRYDR
 AHSNPDFLPVDNCLQSVLGQRVDL (SEQ ID NO:502), and
 10 PEDFQMNYDLWLE REV FSKPISWEELLQ (SEQ ID NO:503). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 15 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

The translation product of this gene shares sequence homology with a *C. elegans* protein (gi|1086830 coded for by *C. elegans* cDNA yk20f8.5).

20 This gene is expressed primarily in T-cells, and to a lesser extent in tumor
 tissue including glioblastoma, menangioma, and Wilm's tumor.

Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 25 diseases of the immune system, including autoimmune conditions such as rheumatoid
 arthritis, inflammatory disorders and cancer. Similarly, polypeptides and antibodies
 directed to these polypeptides are useful in providing immunological probes for
 differential identification of the tissue(s) or cell type(s). For a number of disorders of
 the above tissues or cells, particularly of the immune system, expression of this gene
 30 at significantly higher or lower levels may be routinely detected in certain tissues or
 cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g.
 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell

sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

5 NO: 260 as residues: Thr-9 to Ser-14.

The tissue distribution in T-cells indicates that the protein product of this gene is useful for the diagnosis and/or modulation of immune function disorders, including rheumatoid arthritis and inflammatory responses. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other
10 processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in T cells also strongly indicates a role for this protein
15 in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1388 of SEQ ID NO:22, b is an integer of 15 to 1402, where both a and b correspond to the positions of nucleotide
25 residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

30 This gene is expressed primarily in placenta, and to a lesser extent in fetal liver and bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for the diagnosis of hematological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematological and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. placental, immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver, and bone marrow indicates that the protein product of this gene is useful as a growth factor for hematopoietic stem cells or progenitor cells in the treatment of chemotherapy patients or kidney disease. Furthermore, the tissue distribution in placenta indicates that the protein product of this gene is useful for the diagnosis and/or treatment of vascular or reproductive disorders. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1033 of SEQ ID NO:23, b is an integer of 15 to 1047, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

10 FEATURES OF PROTEIN ENCODED BY GENE NO: 14

This gene is expressed primarily in stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of hematopoietic disorders including cancer, neutropenia, anemia, and thrombocytopenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in stromal cells indicates that the protein product of this gene is useful as a growth factor for hematopoietic stem cells or progenitor cells, in particular following chemotherapy treatment. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture,

bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may
5 have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
15 formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:24, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 15

The translation product of this gene shares sequence homology with epsilon-COP from *Bos taurus*, which is thought to be important as a component of coatamer, a complex of seven proteins, that is the major component of the non-clathrin
25 membrane coat.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
MAPPAPGPASGGSGEVDELFDVKNAFYIGSYQQCINEAXXVKLSSPERDVER
DVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHESRRDSIVAEL
30 DREMSRSXDVTNTTFLMAASIYLDQNPDAALRALHQGDSLECTAMTVQIL
LKLDRLDLARKELKRMQDLDEDATLTQLATAWVSLATGGEKLQDAYYIFQE
MADKCSPTLLLLNGQAACHMAQGRWEAAEGLLQEALDKDSGYPETLVNLIV

- LSQHLGKPPEVTNRYLSQLKDAHRSHPFKEYQAKENDFDRLVLQYAPSABE
GPESGP (SEQ ID NO:504),
- RDVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHESRRDS
IVAELDREMSRSXDVTNTTFLMAASIYLHDQNPDAALRALHQGDSLECTAM
5 TVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWVSLATGGEKLQDAY
YIFQEMADKCSPTLLLLNGQAACHMAQGRWEAAEGLLQEALDKDSGYPETL
VNLIVLSQHLGKPPEVTNRYLSQLKDAHRSHPFKEYQAKENDFDRLVLQYA
PSA (SEQ ID NO:505),
- MAPPAPGPASGGSGEVDLFDVKNFYIGSYQQCINEAXXVKLSSPER (SEQ
10 ID NO:506),
- DVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHES (SEQ
ID NO:507),
- RRDSIVAELDREMSRSXDVTNTTFLMAASIYLHDQNPDAALRALHQG (SEQ
ID NO:508),
- 15 DSLECTAMTVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWVS (SEQ
ID NO:509),
- LATGGEKLQDAYYIFQEMADKCSPTLLLLNGQAACHMAQGRWEAAEG
(SEQ ID NO:510),
- LLQEALDKDSGYPETLVNLIVLSQHLGKPPEVTNRYLSQLKDAHRSH (SEQ
20 ID NO:511), FIKEYQAKENDFDRLVLQYAPSABEAGPELGP (SEQ ID NO:512),
RDVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHE (SEQ
ID NO:513),
- SRRDSIVAELDREMSRSXDVTNTTFLMAASIYLHDQNPDAALRALHQ (SEQ
ID NO:514),
- 25 GDSLECTAMTVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWV (SEQ
ID NO:515),
- SLATGGEKLQDAYYIFQEMADKCSPTLLLLNGQAACHMAQGRWEAAE (SEQ
ID NO:516), GLLQEALDKDSGYPETLVNLIVLSQHLGKPPEVTNRYL (SEQ ID
NO:517), SQLKDAHRSHPFKEYQAKENDFDRLVLQYAPSA (SEQ ID NO:518),
- 30 or
- NRYRESWSLQVPVRNSGSTHASERNGASGPRPGLRRLRGRRRAVRRKERL
LHRQLPAVHKR (SEQ ID NO:519). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides of the invention are useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in activated monocytes and T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunomodulation, specifically relating to transport problems in these cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in activated monocytes and T-cells combined with the homology to epsilon-COP indicates that the protein product of this gene is useful for treating and/or diagnosing problems with the cellular transport of proteins that may result in immunologic dysfunction. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or

protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1194 of SEQ ID NO:25, b is an integer of 15 to 1208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 16

The translation product of this gene shares sequence homology with an RNA helicase which is thought to be important in polynucleotide metabolism. The translation product of this contig exhibits good homology to the LbeIF4A antigen of *Leishmania braziliensis*. The LbeIF4A antigen, or immunogenic portions of it, can be used to induce protective immunity against leishmaniasis, specifically *L. donovani*, *L. chagasi*, *L. infantum*, *L. major*, *L. braziliensis*, *L. panamensis*, *L. tropica* and *L. guyanensis*. It can also be used diagnostically to detect *Leishmania* infection or to stimulate a cellular and/or humoral immune response or to stimulate the production of interleukin-12. The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in colon cancer, and to a lesser extent, in pituitary.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of cancers particularly of the colon. Similarly, polypeptides and

antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal system, expression of this gene at significantly higher or lower levels may be routinely
5 detected in certain tissues or cell types (e.g. colon, pituitary, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 264 as residues: Glu-93 to Ala-98, Gln-150 to Leu-156, Leu-220 to Leu-231, Leu-268 to Arg-273, Val-324 to Pro-341, Arg-372 to Asn-380, Ser-405 to Gly-410, Phe-426 to Ala-433, Glu-458 to Asp-470, and/or Arg-506 to Ser-547.

The tissue distribution in colon cancer, combined with the homology to RNA
15 helicase indicates that the protein product of this gene is useful for the development of diagnostic tests for colon cancer or other gastrointestinal or metabolic disorders. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1908 of SEQ ID NO:26, b is an integer of 15 to 1922, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

The translation product of this contig has sequence homology to a cytoplasmic protein that binds specifically to JNK, designated the JNK interacting protein-1 or JIP-1 in *Mus musculus*. JIP-1 caused cytoplasmic retention of JNK and inhibition of JNK-regulated gene expression. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

10 APGXGWRGSLGEPPPPRASLSSDTSALSYDSVKYTLVVDEHAQLELV
SLRRASETTVTRVTLPPS (SEQ ID NO:520),
APGXGWRGSLGEPPPPRASLSSDTSALSY (SEQ ID NO:521), or
DSVKYTLVVDEHAQLELVSLRRASETTVTRVTLPPS (SEQ ID NO:522).

Moreover, fragments and variants of these polypeptides (such as, for example,
15 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
encoding these polypeptides) are encompassed by the invention. Antibodies that
bind polypeptides of the invention are also encompassed by the invention.

20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain, including pituitary, cerebellum,
frontal cortex, and fetal brain, and to a lesser extent in the cortex or the kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
25 and for diagnosis of the central nervous system disorders including ischemia,
epilepsy, Parkinson's disease, and schizophrenia. Similarly, polypeptides and
antibodies directed to these polypeptides are useful in providing immunological
probes for differential identification of the tissue(s) or cell type(s). For a number of
disorders of the above tissues or cells, particularly of the central nervous system,
30 expression of this gene at significantly higher or lower levels may be routinely
detected in certain tissues or cell types (e.g. brain, kidney, cancerous and wounded
tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Furthermore, the translation product of this contig may suppress the effects of the

- 5 JNK signaling pathway on cellular proliferation, including transformation by the Bcr-Abl oncogene.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 265 as residues: Pro-6 to Ser-26, Ala-30 to Asp-41, Gly-55 to Ser-61, Gly-74 to Thr-80, Tyr-117 to Ala-123, Tyr-167 to Asp-172, Ala-212 to Cys-223, and/or Pro-10 239 to Tyr-244.

The tissue distribution in brain indicates that the protein product of this gene is useful for the enhanced survival and/or differentiation of neurons as a treatment for neurodegenerative disease. Furthermore, the tissue distribution indicates that the translation product of this gene may be involved in neuronal survival; synapse15 formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are20 related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general25 formula of a-b, where a is any integer between 1 to 1937 of SEQ ID NO:27, b is an integer of 15 to 1951, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

30 **FEATURES OF PROTEIN ENCODED BY GENE NO: 18**

The translation product of this gene shares sequence homology with a liver stage antigen from a protozoan parasite.

This gene is expressed primarily in fetal tissue, and to a lesser extent, in activated T-cells and other immune cells.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities and diseases of immune function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid
15 and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells, combined with the homology to a protozoan antigen indicates that the protein product of this gene is useful for the treatment
20 and/or immune modulation of parasitic infections. Furthermore, expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
25 related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
30 formula of a-b, where a is any integer between 1 to 3975 of SEQ ID NO:28, b is an integer of 15 to 3989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- MKAIGIEPSLATYHHIIRLFDQPGDPLKRSSFITYDIMNELMGKRFSPKDPDDD
 KFFQSAMSICSSLRDLELAYQVHGLLKTGDNWKFIGPDQHRNFYYSKFFDLIC
 LMEQIDVTLKWYEDLIPSAYFPHSQTMHLLQALDVANRLEVIPKIWER (SEQ
 10 ID NO:523),
- KDSKEYGHTFRSDLREEILMLMARDKHPPELQVAFADCAADIKSAYESQPIRQ
 TAQDWPATSLNCIAILFLRAGRTQEAWKMLGLFRKH NKIPRSELLNELMDSA
 KVSNSPSQAIEVVELASAFSLPICEGLTQRVMSDFAINQEKEALSNLTALTSD
 SDTDSSSDSDSDTSEGK (SEQ ID NO:524),
- 15 MKAIGIEPSLATYHHIIRLFDQPGDPLKRSSFITYDIMNELMGKRFSPK (SEQ ID
 NO:525),
- DPDDDKFFQSAMSICSSLRDLELAYQVHGLLKTGDNWKFIGPDQHRNFY
 (SEQ ID NO:526), YSKFFDLICLMEQIDVTLKWYEDLIPSA (SEQ ID NO:527),
 YFPHSQTMHLLQALDVANRLEVIPKIWER (SEQ ID NO:528),
- 20 KDSKEYGHTFRSDLREEILMLMARDKHPPELQVAFADCAADIKSAY (SEQ ID
 NO:529),
- ESQPIRQTAQDWPATSLNCIAILFLRAGRTQEAWKMLGLFRKH NKIPRSE
 (SEQ ID NO:530),
- LLNELMDSAKVSNSPSQAIEVVELASAFSLPICEGLTQRVMSDFAIN (SEQ ID
 25 NO:531), or QEKEALSNLTALTSDSDTDSSSDSDSDTSEGK (SEQ ID NO:532).
- Moreover, fragments and variants of these polypeptides (such as, for example,
 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 30 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.
 Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in stromal and CD34 depleted bone marrow cells, and to a lesser extent in tissues of embryonic origin.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of hematopoietic origin including cancers and immune dysfunction.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 267 as residues: Ser-28 to Gln-34.

The tissue distribution in stromal and CD34 depleted bone marrow cells indicates that the protein product of this gene is useful as a growth factor for hematopoietic stem cells or progenitor cells which may be useful in the treatment of chemotherapy patients suffering from neutropenia. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection,

inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3721 of SEQ ID NO:29, b is an integer of 15 to 3735, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

In specific embodiments, polypeptides of the invention comprise, or
20 alternatively consists of, an amino acid sequence selected from the group:
MSSDNESDIEDLKLRLRLDKHLKEIQDLQSRQKHEIESLYTKLGKVPPA
VIIPPAAPLSGRRRRPTKSKGSKSSRSSSLGNKSPQLSGNLSGQSAASVLHPQQ
TLHPPGNIPESGQNQLLQPLKPSRSSDNL YSAFTSDGAISVPSLSAPGQGTSSSTN
TVGATVNSQAAQAQPPAMTSSRKGFTTDDLHKLVDNWARDAMNLSGRRGS
25 KGHMNYEGPGMARKFSAPGQLCISMTSNLGGAPISAASATSLGHFTKSMCP
PQQYGFPA TPFGAQWSGTGGPAPQPLGQFQPVGTASLQNFNISNLQKSISNPP
GSNLRTT (SEQ ID NO:533),
IQDLQSRQKHEIESLYTKLGKVPPAVIIPPAAPLSGRRRRPTKSKGSKSSRSSSL
GNKSPQLSGNLSGQSAASVLHPQQTLHPPGNIPESGQNQLLQPLKPSRSSDNL
30 YSAFTSDGAISVPSLSAPGQGT SST (SEQ ID NO:534),
TSDGAISVPSLSAPGQGTSSSTNTVGATVNSQAAQAQPPAMTSSRKGFTTDDL
H (SEQ ID NO:535),

- KGHMNYEGPGMARKFSAPGQLCISMTSNLGGAPISAASATSLGHFTK (SEQ ID NO:536), QPLKPSPSSDNL YSAFTSDGAISVPSLSAPG (SEQ ID NO:537), MSSDNESDIEDLDKLELRRRLRD KHLKEIQDLQSRQKHEIESLYTKLGKVP (SEQ ID NO:538),
- 5 PAVIIPPAAPLSGRRRRPTKSKGSKSSRSSSLGNKSPQLSGNLSGQS (SEQ ID NO:539),
- AASVLHPQQTLHPPGNIPESGQNQLLQPLKPSPSSDNL YSAFTSDGAISV (SEQ ID NO:540), PLSAPGQGTSSNTVVGATVNSQAAQAQPPAMTSSRKGTFTDDL (SEQ ID NO:541),
- 10 HKLVDNWARDAMNLSGRRGSKGHMNYEGPGMARKFSAPGQLCISMT (SEQ ID NO:542),
- SNLGGAPISAASATSLGHFTKSMCPPQQYGFPATPFGAQWSGTGG (SEQ ID NO:543), and PAPQPLGQFQPVGTASLQNFNISNLQKSISNPPGSNLRTT (SEQ ID NO:544). Moreover, fragments and variants of these polypeptides (such as, for
- 15 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.
- 20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in fetal liver and tissues associated with the CNS.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
- 25 liver and CNS diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell
- 30 types (e.g. liver, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression

level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 268 as residues: Gln-26 to Lys-34.

5 The tissue distribution in fetal liver and neural tissues indicates that the protein product of this gene is useful for the diagnosis and treatment for liver diseases such as hepatocellular carcinomas and diseases of the CNS. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, 10 liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells), as well as the detection and treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic 15 disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of 20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1653 of SEQ ID NO:30, b is an 25 integer of 15 to 1667, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

30

The translation product of this gene shows sequence homology to two recently cloned genes, karyopherin beta 3 and Ran_GTP binding protein 5. (See Genbank

Accession Nos. gi|2102696 and gnl|PID|e328731.) The Ran_GTP binding protein is related to importin-beta, the key mediator of nuclear localization signal (NLS)-dependent nuclear transport. Based on homology, it is likely that this gene may demonstrate activity similar to the RAN_GTP binding protein.

5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

VRVAAAESMXLLLECA XVRGPEYLTQMW HFMCDALIK AIGTEPDS DVLSEI
MHSFAK (SEQ ID NO:545). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%,
10 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the
15 invention.

This gene is expressed in thymus tissue, and to a lesser extent in stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
20 immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell
25 types (e.g. immune, thymus, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in thymus indicates that the protein product of this gene is useful for the diagnosis and treatment for immune disorders. Furthermore, the polypeptides or polynucleotides of the present invention are also useful in the

treatment, prophylaxis, and detection of thymus disorders, such as Graves Disease, lymphocytic thyroiditis, hyperthyroidism, and hypothyroidism. Additionally, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1394 of SEQ ID NO:31, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

The translation product of this gene shares sequence homology with a natural resistance-associated macrophage protein 2 from Homo sapiens (gi|3152690 (AF064484)), which is thought to function as a macrophage-specific membrane transport protein. This gene is expressed primarily in prostate and osteoclastoma tissues. In specific embodiments, polypeptides of the invention comprise, or

30

alternatively consists of, an amino acid sequence selected from the group:

MEINNQNCFIVIDLVRTVMENGVEGLLIFGAFLPESWLIGVRCSEPPKALLLIL

AHSQKRRLDGWSFIRHLRVHYCVSLTIHFS (SEQ ID NO:546),

GGREANKXFFIESCIALFVSFIINVVVSVFAEXFFGXTNEQVVEVCTNTSSPH

5 AGLFPKDNSTLAVDIYKGGVVLGCYFGPAALYTWAVGILAAGQSST (SEQ ID
NO:547), GGREANKXFFIESCIALFVSFIINVVVSVFAEXFFGXTNEQVVE

(SEQ ID NO:548), and/or

VCTNTSSPHAGLFPKDNSTLAVDIYKGGVVLGCYFGPAALYTWAVGILAAGQ

SST (SEQ ID NO:549). Moreover, fragments and variants of these polypeptides

10 (such as, for example, fragments as described herein, polypeptides at least 80%, 85%,
90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
encoded by the polynucleotide which hybridizes, under stringent conditions, to the
polynucleotide encoding these polypeptides) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the
15 invention. Polynucleotides encoding these polypeptides are also encompassed by the
invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome
12. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 12.

20 This gene is expressed primarily in fetal liver/spleen, fetal brain, and to a
lesser extent in placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
25 immune, developmental, hepatic, or bone and prostate diseases, and cancers,
particularly of the bone and prostate. Similarly, polypeptides and antibodies directed
to these polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the bone and prostate systems, expression of this gene
30 at significantly higher or lower levels may be routinely detected in certain tissues or
cell types (e.g. bone, prostate, cancerous and wounded tissues) or bodily fluids (e.g.
lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell

sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in bone indicates that the protein product of this gene is
5 useful for the diagnosis and treatment of bone and prostate disorders, especially
cancers of those systems. Elevated levels of expression of this gene product in
osteoclastoma indicates that it may play a role in the survival, proliferation, and/or
growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such
conditions as osteoporosis. Moreover, the protein product of this gene is useful for
10 the treatment and diagnosis of hematopoietic related disorders such as anemia,
pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are
important in the production of cells of hematopoietic lineages. The uses include bone
marrow cell ex vivo culture, bone marrow transplantation, bone marrow
reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may
15 also be involved in lymphopoiesis, therefore, it can be used in immune disorders such
as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene
product may have commercial utility in the expansion of stem cells and committed
progenitors of various blood lineages, and in the differentiation and/or proliferation of
various cell types. Protein, as well as, antibodies directed against the protein may
20 show utility as a tumor marker and/or immunotherapy targets for the above listed
tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
available and accessible through sequence databases. Some of these sequences are
related to SEQ ID NO:32 and may have been publicly available prior to conception of
25 the present invention. Preferably, such related polynucleotides are specifically
excluded from the scope of the present invention. To list every related sequence is
cumbersome. Accordingly, preferably excluded from the present invention are one or
more polynucleotides comprising a nucleotide sequence described by the general
formula of a-b, where a is any integer between 1 to 3172 of SEQ ID NO:32, b is an
30 integer of 15 to 3186, where both a and b correspond to the positions of nucleotide
residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

5 This gene shares sequence homology with the FK506-binding protein (FKBP-
13) family, a known cytosolic receptor for the immunosuppressants FK506 and
rapamycin. Recently, another group has cloned a very similar gene, recognizing the
homology to the FK506-binding protein family, calling their gene FKBP23 (See
Genbank Accession No. 2827255.). Contact of cells with supernatant expressing the
product of this gene increases the permeability of both prostate stromal cells and
10 dermal fibroblasts to calcium. Thus, it is likely that the product of this gene is
involved in a signal transduction pathway that is initiated when the product of this
gene binds receptors on the surface of stromal cells and dermal fibroblast cells. Thus,
polynucleotides and polypeptides have uses which include, but are not limited to,
activating stromal and fibroblast cells.

15 This gene is expressed primarily in lymphoid tissues and stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample,
especially for those susceptible to immune suppressant therapies and for diagnosis of
diseases and conditions which include, but are not limited to, immune suppressant
20 disorders. Similarly, polypeptides and antibodies directed to these polypeptides are
useful in providing immunological probes for differential identification of the
tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
particularly of the immune system, expression of this gene at significantly higher or
lower levels may be routinely detected in certain tissues or cell types (e.g. immune,
25 cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine,
synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
the expression level in healthy tissue or bodily fluid from an individual not having the
disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 271 as residues: Ala-19 to Val-31, Arg-38 to Gly-49, Ala-61 to Lys-66, Tyr-68

to Pro-78, Gly-116 to Ala-121, Asp-154 to Ser-162, Glu-173 to Gln-186, Phe-194 to Gly-203, and/or Pro-207 to Val-212.

The tissue distribution in lymphoid tissues and stromal cells, the biological activity data, combined with the homology to FKBP-12 and -13 indicates that the protein product of this gene is useful for the diagnosis and treatment of immune suppressant disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:33, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

20

The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

This gene is expressed primarily in the brain and in the retina.

25

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and ocular associated disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the central nervous system, expression of this gene at significantly higher or lower levels may be

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5 routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.; the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 272 as residues: Cys-34 to Asp-40.

10 The tissue distribution in retina indicates that the protein product of this gene is useful for the treatment and/or detection of eye disorders including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma. Expression in the brain indicates a role in the is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1778 of SEQ ID NO:34, b is an integer of 15 to 1792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

30 This gene shows sequence homology to a newly identified class of proteins expressed in the nervous system, called stathmin family. (See Genbank Accession No. 2585991; see also Eur. J. Biochem. 248 (3), 794-806 (1997).) The stathmin

family appears to be an ubiquitous phosphoprotein involved as a relay integrating various intracellular signaling pathways. These pathways affect cell proliferation and differentiation.

- In specific embodiments, polypeptides of the invention comprise, or
 5 alternatively consists of, an amino acid sequence selected from the group:
 QDKHAEVRKNKELKEEASR (SEQ ID NO:550),
 QQDLSPWAAPVGCPLXXASXTCHXLPLSGCLRRQSXSLPVVAXLCFWFSCPL
 ASLFVPGQPCVTCPFPSLPFQDKHAEVRKNKELKEEASR (SEQ ID NO:551).
 Moreover, fragments and variants of these polypeptides (such as, for example,
 10 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.
 15 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed highly in brain tissues.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
 20 neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell
 25 types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 30 The tissue distribution in brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease,

schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 882 of SEQ ID NO:35, b is an integer of 15 to 896, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 26

The polynucleotide sequence of this gene contains a domain similar to a Flt3 ligand peptide.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
PTRCCTTQPCRSSARRPCWVPMVPSPEGREXQPTCPS (SEQ ID NO:552).
Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene may have activity as binding to Flt3 receptors, a process known to promote angiogenesis and/or lymphangiogenesis.

This gene is expressed in human tonsil, and to a lesser extent in teratocarcinoma, placenta, colon carcinoma, and fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the tonsil, as well as cancers, such as colon, reproductive, and kidney
5 cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tonsils, colon, reproductive organs, and kidneys, expression of this gene at significantly higher or lower levels may be routinely detected in certain
10 tissues or cell types (e.g. immune, tonsils, colon, kidney, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 274 as residues: Pro-22 to Glu-33.

The tissue distribution in tonsils, several cancers, and fetal tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of diseases of the tonsil or colon, such as tonsillitis, inflammatory diseases involving
20 nose and paranasal sinuses, especially during the infection of influenza, adenoviruses, parainfluenza, or rhinoviruses, for example. The gene may also be useful in the diagnosis and treatment of neoplasms of nasopharynx or colon origins. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 898 of SEQ ID NO:36, b is an

integer of 15 to 912, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MKRSLNENSARSTAGCLPVPLFNQKKRNRQPLTSNPLKDDSGISTPSDNYDFP
 10 PLPTDWAWEAVNPEXAPVMKTVDTGQIPHSVSRPLRSQDSVFNSIQSNTGRS
 QGGWSYRDGNKNTSLKTWXXKNDFKPQCKRTNLVANDGKNSCPMSSGAQQ
 QKQLRTPEPPNLSRNKETELLRQTHSSKISGCTMRGLDKNSALQTLKPNFQQN
 QYKXQMLDDIPEDNTLKETSLYQLQFKEKASSLRIISAVIESMKYWREHAQKT
 VLLFEVLAVLDSAVTPGPYYSKTFLMRDGKNTLPCVFYEIDRELRLIRGRVH
 15 RCVGNYDQKKNIFQCVSVRPASVSEQKTFQAFVKIADVEMQYYINVMNET
 (SEQ ID NO:553),
 SQDSVFNSIQSNTGRSQGGWSYRDGNKNTSLKTWXXKNDFKPQCKR (SEQ ID
 NO:554), NKETELLRQTHSSKISGCTMRGLDKNSALQTLKPNF (SEQ ID
 NO:555),
 20 SSLRIISAVIESMKYWREHAQKT VLLFEVLAVLDSAVTPGPYYSKTFLM (SEQ
 ID NO:556), and/or
 PRLIRGRVHRCVGNYDQKKNIFQCVSVRPASVSEQKTFQAFV (SEQ ID
 NO:557). Moreover, fragments and variants of these polypeptides (such as, for
 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,
 25 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 This gene is expressed primarily in human testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive disorders, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human testes indicates that the protein product of this gene is useful as a hormone with reproductive or other systemic functions; contraceptive development; male infertility of testicular causes, such as Klinefelter's syndrome, varicocele, orchitis; male sexual dysfunctions; testicular neoplasms; and inflammatory disorders such as epididymitis. Furthermore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:37, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 28

This gene is expressed primarily in apoptotic T-cell.

Polynucleotides and polypeptides of the invention are useful as reagents for
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases relating to T cells, as well as cancer in general. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
15 disorders of the above tissues or cells, particularly of the disorders of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such
20 a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in apoptotic T-cells indicates that the protein product of this gene is useful for the detection and/or treatment of disorders of the immune system. Moreover, since the gene was isolated from an apoptotic cell, and based on
25 the understanding of the relationship of apoptosis and cancer, it is likely that this gene may play a role in the genesis of cancer. Furthermore, expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:38, b is an integer of 15 to 872, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

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This gene is expressed primarily in human tonsils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

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The tissue distribution in human tonsils indicates that the protein product of this gene is useful for the diagnosis and treatment of gastrointestinal diseases.

Alternatively, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and treatment of a variety of immune system disorders.

Expression of this gene product in tonsils indicates a role in the regulation of the

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proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other

processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or
- 10 proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
- 15 related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
- 20 formula of a-b, where a is any integer between 1 to 798 of SEQ ID NO:39, b is an integer of 15 to 812, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO:30

- 25 This gene is expressed primarily in human T-cells, and to a lesser extent, in human colon carcinoma.

The translation product of this gene shares sequence homology with C44C1.2 gene product of *Caenorhabditis elegans*.

- Preferred polypeptides of the present invention comprise, or alternatively
- 30 consist of, one, two, three, four, five, six, seven or all seven of the immunogenic epitopes shown in SEQ ID NO:278 as residues: Leu-21 to Ala-30, Ser-38 to Asp-47, Pro-87 to Asp-94, Leu-197 to Thr-204, Pro-256 to Ser-262, Thr-277 to Arg-282,

and/or Thr-293 to Trp-303. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides.

5 Additionally, preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, or both of the immunogenic epitopes shown in SEQ ID NO:1232 as residues: Gly-204 to Gly-234 and Arg-202 to Asp-236.

Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides.

10 In additional nonexclusive embodiments, preferred polypeptides of the invention also comprise, or alternatively consist of, one or more of the following amino acid sequences: Gly-188 to Val-203, Gly-188 to Thr-204, Thr-204 to Lys-257, Asp-280 to Leu-362 of SEQ ID 278 and Gly-204 to Gly-234 of SEQ ID NO: 1232. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides.

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

GVFRPCVCGRPASLTCSPLDPEVGPYCDTPTMRTLNFNLLWLALACSPVHTTLS
 KSDAKKAASKTLLEKSQFSDKPVQDRGLVVTDLKAESVVLEHRSYCSAKAR
 DRHFAGDVLGYVTPWNSHGYDVTKVFGSKFTQISPVWLQLKRRGREMFVET
 20 GLHDVDQGWMAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDEIEELSK
 TVVQVAKNQHFDFGVVEVWNQLLSQKRVGLIHMLTHLAEALHQAARLLALL
 VIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSLMTYDYSTAHPGPNAPLSWV
 RACVQVLDPKXKWRTKSSWGSTMXWTXRXPDARXPVVGXRXIQLKDH
 XPRMVLDLSPQ (SEQ ID NO:558),
 25 TCSPLDPEVGPYCDTPTMRTLNFNLLWLALACSPVHTTLS (SEQ ID NO:559),
 LVVTDLKAESVVLEHRSYCSAKARDRHFAGDVLGYVTPWNSHGYDVTKVFGSKF (SEQ ID NO:560),
 REMFEVETGLHDVDQGWMAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDE (SEQ ID NO:561),
 30 HFDGFVVEVWNQLLSQKRVGLIHMLTHLAEALHQAARLLALLVIPPAITPGTDQLGM (SEQ ID NO:562), and
 DGFSLMTYDYSTAHPGPNAPLSWVRACVQVLDPKXKWRTKSSWGSTMXWTXRXPDARXPVVGXRXIQLKDH (SEQ ID NO:563).

ID NO:563). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
5 encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In additional nonexclusive embodiments, polynucleotides of the invention comprise or alternatively consist of, one or more of the following sequences:

10 GGCACGAGCGTTTTCCGGCCGTGCGTTTGTGGCCGTCCGGCCTCCC
TGACATGCAGCCCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCT
ACCATGCGGACACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCT
GTTCACTACCCTGTCAAAGTCAGATGCCAAAAAGCCGCCTCAAAGAC
GCTGCTGGAGAAGAGTCAGTTTTTCAGATAAGCCGGTGCAAGACCGGGGTT
15 TGGTGGTGACGGACCTCAAAGCTGAGAGTGTGGTTCTTGAGCATCGCAGC
TACTGCTCGGCAAAGGCCCGGGACAGACACTTTGCTGGGGATGTACTGGG
CTATGTCACTCCATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTG
GGAGCAAGTTCACACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGT
GGCCGTGAGATGTTTGAGGTCACGGGCCTCCACGACGTGGACCAAGGGTG
20 GATGCGAGCTGTCAGGAAGCATGCCAAGGGCCTGCACATAGTGCCTCGGC
TCCTGTTTGAGGACTGGACTTACGATGATTTCCGGAACGTCTTAGACAGTG
AGGATGAGATAGAGGAGCTGAGCAAGACCGTGGTCCAGGTGGCAAAGAA
CCAGCATTTGATGGCTTCGTGGTGGAGGTCTGGAACCAGCTGCTAAGCC
AGAAGCGCGTGGGCCTCATCCACATGCTCACCCACTTGGCCGAGGCTCTG
25 CACCAGGCCCGGCTGCTGGCCCTCCTGGTCATCCCGCCTGCCATCACCCCC
GGGACCGACCAGCTGGGCATGTTACGCACAAGGAGTTTGAGCAGCTGGC
CCCCGTGCTGGATGGTTTCAGCCTCATGACCTACGACTACTCTACAGCGCA
TCAGCCTGGCCCTAATGCACCCCTGTCCTGGGTTCGAGCCTGCGTCCAGGT
CCTGGACCCGAAGTCCAAGTGGCGAAGCAAAATCCTCCTGGGGCTCAACT
30 TCTATGGTACATCCAGACACTGAAGGACCACAGGCCCGGATGGTGTGGG
ACAGCCAGGTCTCAGAGCACTTCTTCGAGTACAAGAAGAGCCGCAGTGGG
AGGCACGTCGTCTTCTACCCAACCCTGAAGTCCCTGCAGGTGCGGCTGGA

GCTGGCCCCGGGAGCTGGGCGTTGGGGTCTCTATCTGGGAGCTGGGCCAGG
GCCTGGACTACTTCTACGACCTGCTCTAGGTGGGCATTGCGGCCTCCGCGG
TGGACGTGTTCTTTTCTAAGCCATGGAGTGAGTGAGCAGGTGTGAAATAC
AGGCCTCCACTCCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
5 AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:1228),
GCGCTGGAGCGTTTTCCGGCCGTGCGTTTGTGGCCGTCCGGCCTCCCTGAC
ATGCAGCCCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCTACCA
TGCGGACACTCTTCAACCTCCTCTGGCTTGGCCTGGCCTGCAGCCCTGTTC
ACACTACCCTGTCAAAGTCAGATGCCAAAAAAGCCGCCTCAAAGACGCTG
10 CTGGAGAAGAGTCAGTTTTTCAGATAAGCCGGTGCAAGACCGGGGTTTGGT
GGTGACGGACCTCAAAGCTGAGAGTGTGGTTCTTGAGCATCGCAGCTACT
GCTCGGCAAAGGCCCGGGACAGACACTTTGCTGGGGATGTACTGGGCTAT
GTCACTCCATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTGGGAG
CAAGTTCACACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGTGGCC
15 GTGAGATGTTTGAGGTACGGGCCTCCACGACGTGGACCAAGGGTGGATG
CGAGCTGTCAGGAAGCATGCCAAGGGCCTGCACATAGTGCCTCGGCTCCT
GTTTGAGGACTGGACTTACGATGATTTCCGGAACGTCTTAGACAGTGAGG
ATGAGATAGAGGAGCTGAGCAAGACCGTGGTCCAGGTGGCAAAGAACCA
GCATTTTCGATGGCTTCGTGGTGGAGGTCTGGAACCAGCTGCTAAGCCAGA
20 AGCGCGTGACCGACCAGCTGGGCATGTTACGCACAAGGAGTTTGAGCAG
CTGGCCCCCGTGCTGGATGGTTTCAGCCTCATGACCTACGACTACTCTACA
GCGCATCAGCCTGGCCCTAATGCACCCCTGTCCTGGGTTCGAGCCTGCGTC
CAGGTCCTGGACCCGAAGTCCAAGTGGCGAAGCAAAATCCTCCTGGGGCT
CAACTTCTATGGTATGGACTACGCGACCTCCAAGGATGCCCCTGAGCCTG
25 TTGTCGGGGCCAGGTACATCCAGACACTGAAGGACCACAGGCCCCGGATG
GTGTGGGACAGCCAGGYCTCAGAGCACTTCTTCGAGTACAAGAAGAGCCG
CAGTGGGAGGCACGTCGTCTTCTACCCAACCCTGAAGTCCCTGCAGGTGC
GGCTGGAGCTGGCCCCGGGAGCTGGGCGTTGGGGTCTCTATCTGGGAGCTG
GGCCAGGGCCTGGACTACTTCTACGACCTGCTCTAGGTGGGCATTGCGGC
30 CTCCGCGGTGGACGTGTTCTTTTCTAAGCCATGGAGTGAGTGAGCAGGTG
TGAAATACAGGCCTNCACTCCGTTCAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAACTCGAG (SEQ ID NO: 1229),

GGCGTTTTCCGGCCGTGCGTTTGTGGCCGTCCGGCCTCCCTGACATGCAGC
CCTCTGGACCCCGAGGTTGGACCCCTACTGTGACACACCTACCATGCGGAC
ACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCTGTTCACTAC
CCTGTCAAAGTCAGATGCCAAAAAGCCGCCTCAAAGACGCTGCTGGAGA
5 AGAGTCAGTTTTTCAGATAAGCCGGTGCAAGACCGGGGTTTGGTGGTGACG
GACCTCAAAGCTGAGAGTGTGGTTCTTGAGCATCGCAGCTaCTGCTcGGCA
AAGGCCCGGGACAGACACTTTGCTGGGGATGTACTGGGCTATGTCACTCC
ATGGAACAGCCATGGCTACGATGTACCAAGGTCTTTGGGAGCAAGTTCA
CACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGTGGCCGTGAGATG
10 TTTGAGGTCACGGGCCTCCACGACGTGGACCAAGGGTGGATGCGAGCTGT
CAGGAAGCATGCCAAGGGCCTGCACATAGTGCCTCGGCTCCTGTTTGAGG
ACTGGACTTACGATGATTTCCGGAACGTCTTAGACAGTGAGGATGAGATA
GAGGAGCTGAGCAAGACCGTGGTCCAGGTGGCAAAGAACCAGCATTTCG
ATGGCTTCGTGGTGGAGGTCTGGAACCAGCTGCTAAGCCAGAAGCGCGTG
15 GGCCTCATCCACATGCTCACCCACTTGGCCGAGGCTCTGCACCAGGCCCCG
GCTGCTGGCCCTCCTGGTCATCCCGCCTGCCATCACCCCCGGGACCGACC
AGCTGGGCATGTTACGCACAAGGAGTTTGAGCAGCTGGCCCCCGTGCTG
GATGGTTTCAGCCTCATGACCTACGACTACTCTACAGCGCATCAGCCTGGc
CCTAATGCACCCcTGTCCTGGGTTCGAGCCTGCGTCCAGGTCCTGGACCCG
20 AARTYCAAGTGGCGAACAAAATCCTCCTGGGGSTCAACTTCTATGGWATG
GACTAMGCGACYTCCAANGGATGCCCGTKARCCTGTTGTCTGGGGSCAGGT
AMATYCAGAMACTGAARGACCACANGCCCCGGATGGTGTGAGACAGCAA
GCCTCAAAG (SEQ ID NO:1230), and
ATAAGAGACAGCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAAC
25 GCGGNCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCT
TTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGT
GAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGT
GAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCG
CGTTGGCCGATTCAATTAATGCAGCTGGCACGACAGGTTTCCCGACTGGAA
30 AGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGG
CACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTG
TGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCC

AAGCTCGAAATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTCCACCG
CGGTGGCGGCCGCTCTAGAACTAGTGGATCCCCCGGGCTGCAGGAATTCG
GCACGAGGTCCGGCCTCCCTGACATGCAGATTTCCACCCAGAAGACAGAG
AAGGAGCCAGTGGTCATGGAATGGGCTGGGGTCAAAGACTGGGTGCCTG
5 GGAGCTGAGGCAGCCACCGTTTCAGCCTGGCCAGCCCTCTGGACCCCGAG
GTTGGACCCTACTGTGACACACCTACCATGCGGACACTCTTCAACCTCCTC
TGGCTTGCCCTGGCCTGCAGCCCTGTTCACTACTACCCTGTCAAAGTCAGAT
GCCAAAAAAGCCGCCTCAAAGACGCTGCTGGAGAAGAGTCAGTTTTTCAGA
TAAGCCGGTGCAAGACCGGGGTTTGGTGGTGACGGACCTCAAAGCTGAGA
10 GTGTGGTTCTTGAGCATCGCAGCTACTGCTCGGCAAAGGCCCGGGACAGA
CACTTTGCTGGGGATGTACTGGGCTATGTCACTCCATGGAACAGCCATGG
CTACGATGTCACCAAGGTCTTTGGGAGCAAGTTCACACAGATCTCACCCG
TCTGGCTGCAGCTGAAGAGACGTGGCCGTGAGATGTTTGAGGTCACGGGC
CTCCACGACGTGGACCAAGGGTGGATGCGAGCTGTCAGGAAGCATGCCA
15 AGGGCCTGCACATAGTGCCTCGGCTCCTGTTTGAGGACTGGACTTACGAT
GATTTCCGGAACGTCTTAGACAGTGAGGATGAGATAGAGGAGCTGAGCA
AGACCGTGGTCCAGGTGGCAAAGAACCAGCATTTCGATGGCTTCGTGGTG
GAGGTCTGGAACCAGCTGCTAAGCCAGAAGCGCGTGGGCCTCATCCACAT
GCTCACCCACTTGGCCGAGGCTCTGCACCAGGCCCGGCTGCTGGCCCTCC
20 TGGTCATCCCGCCTGCCATCACCCCGGGACCGACCAGCTGGGCATGTTT
ACGCACAAGGAGTTTGAGCAGCTGGCCCCCGTGCTGGATGGTTTCAGCCT
CATGACCTACGACTACTCTACAGCGCATCAGCCTGGCCCTAATGCACCCC
TGTCTTGGGTTCGAGCCTGCGTCCAGGTCCTGGACCCGAAGTCCAAGTGG
CGAAGCAAAATCCTCCTGGGGCTCAACTTCTATGGTACATCCAGACACTG
25 AAGGACCACAGGCCCCGGATGGTGTGGGACAGCCAGGCCTCAGAGCACT
TCTTCGAGTACAAGAAGAGCCGCAGTGGGAGGCACGTCGTCTTCTACCCA
ACCCTGAAGTCCCTGCAGGTGCGGCTGGAGCTGGCCCGGGAGCTGGGCGT
TGGGGTCTCTATCTGGGAGCTGGGCCAGGGCCTGGACTACTTCTACGACC
TGCTCTAGGTGGGCATTGCGGCCTCCGCGGTGGACGTGTTCTTTCTAAGC
30 CATGGAGTGAGTGAGCAGGTGTGAAATACAGGCCTCCACTCCGTAAAAA
AAAAAAAAAAAAAAAAAACTCGAGGGGGGGCCCGGTACCCAATTCGCCC
TATAGTGAGTCGTATTACAATTCACTGGCCGTCGTTTTACAACGTCGTGAC

TGGGAAAACCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCT
 TTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCA
 ACAGTTGCGCAGCCTGAATGGCGAATGGCAAATTGTAAGCGTTAATATTT
 TGTAAAAATTCGCGTTAAATTTTTGTAAATCAGCTCATTTTTTAACCAAT
 5 AGGCCGAAATCGGCAAAATCCCTTATAAATCAAAGAATAGACCGAGAT
 AGGGTTGAGTGTTGNTCCAGTTTGAACAAGAGTCCACTATTAAAGAACG
 TGGACTCCAACGTCAAAGGGCGAAAAACCGNCTATCAGGGCGATGGCCC
 ACTACGTGAACCATCACCTTAATCAAAGTTTTTTGGGGTCGAGGTNCCCC
 TAAAGCACTTAATCGGGAACCC (SEQ ID NO:1231). Polypeptides encoded
 10 by these polynucleotides are also encompassed by the invention, as are antibodies that
 bind to these polypeptides.

In other specific embodiments, polypeptides of the invention comprise, or
 alternatively consists of, an amino acid sequence selected from the group:

MRTLFNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV
 15 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF
 TQISPVWLQLKRRGREMFVETGLHDVDQGWMAVRKHAKGLHIVPRLLFED
 WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVGL
 IHMLTHLAEALHQARLLALLVIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSL
 MTYDYSTAHPGPNAPLSWVRACVQVLDPKSKWRSKILLGLNFYGTSRH
 20 (SEQ ID NO: 1232),
 MRTLFNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV
 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF
 TQISPVWLQLKRRGREMFVETGLHDVDQGWMAVRKHAKGLHIVPRLLFED
 WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVTD
 25 QLGMFTHKEFEQLAPVLDGFSLMTYDYSTAHPGPNAPLSWVRACVQVLDP
 KSKWRSKILLGLNFYGM DYATSKDAREPVVGARYIQTLKDHPRMVWDSQ
 XSEHFFEYKKSRSRGRHVVFYPTLKSQVRLELARELGVGVSIELGQGLDYF
 YDLL (SEQ ID NO: 1233),
 MRTLFNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV
 30 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF
 TQISPVWLQLKRRGREMFVETGLHDVDQGWMAVRKHAKGLHIVPRLLFED
 WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVGL

IHMLTHLAEALHQARLLALLVIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSL
 MTYDYSTAHPGPNAFLSWVRACVQVLDPKXKWRTKSSWGSTMXWTRX
 XPXDARXPVVGXRX (SEQ ID NO: 1234), and

- MRTLFNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV
 5 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF
 TQISPVWLQLKRRGREMFVETGLHDVDQGWMAVRKHAKGLHIVPRLLFED
 WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVGL
 IHMLTHLAEALHQARLLALLVIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSL
 MTYDYSTAHPGPNAFLSWVRACVQVLDPKSKWRSKILLGLNFYGTSRH
 10 (SEQ ID NO: 1235). Moreover, fragments and variants of these polypeptides (such
 as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
 encoded by the polynucleotide which hybridizes, under stringent conditions, to the
 polynucleotide encoding these polypeptides) are encompassed by the invention.
 15 Antibodies that bind polypeptides of the invention are also encompassed by the
 invention. Polynucleotides encoding these polypeptides are also encompassed by the
 invention.

Also preferred are polypeptides, comprising or alternatively consisting of, the
 mature polypeptide which is predicted to consist of residues 23-362 of the foregoing
 20 sequence (SEQ ID NO:278), and biologically active fragments of the mature
 polypeptide (e.g., fragments that inhibit the Mixed Lymphocyte Reaction).
 Polynucleotides encoding these polypeptides are also encompassed by the invention

Figures 1A-B show the nucleotide (SEQ ID NO:40) and deduced amino acid
 sequence (SEQ ID NO: 278) corresponding to this gene.

- 25 Figure 2 shows an analysis of the amino acid sequence (SEQ ID NO: 278).
 Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic
 regions; flexible regions; antigenic index and surface probability are shown, and all
 were generated using the default settings of the recited computer algorithms. In the
 "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the
 30 highly antigenic regions of the protein, i.e., regions from which epitope-bearing
 peptides of the invention can be obtained. Polypeptides comprising, or alternatively

consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 2 are also represented in tabular form in Table 3. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 2, and Table 3: "Res": amino acid residue of SEQ ID NO: 278 and Figures 1A and 1B; "Position": position of the corresponding residue within SEQ ID NO: 278 and Figures 1A and 1B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 2 and/or Table 3, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 3 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 2, but may, as shown in Table 3, be represented or identified by using tabular representations of the data presented in Figure 2. The DNA*STAR computer algorithm used to generate Figure 2 (set on the original default parameters) was used to present the data in Figure 2 in a tabular format (See Table 3). The tabular format of the data in Figure 2 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO:40, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO:40. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:40. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to

about 900, from about 901 to about 950, from about 951 to about 1000, from about 1001 to about 1050, from about 1051 to about 1100, from about 1101 to about 1150 from about 1151 to about 1200, from about 1201 to about 1250, from about 1251 to about 1300, from about 1301 to about 1350, from about 1351 to about 1400, from
5 about 1401 to about 1450, and from about 1451 to about 1515, of SEQ ID NO:40, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional
10 attributes of the corresponding protein.

Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxyl terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-362 where m is an integer
15 from 2 to 356, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:278. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: K-23 to L-362; S-24 to L-362; D-25 to L-362; A-26 to L-362; K-27 to L-362; K-28 to L-362; A-29 to L-362; A-30 to L-362;
20 S-31 to L-362; K-32 to L-362; T-33 to L-362; L-34 to L-362; L-35 to L-362; E-36 to L-362; K-37 to L-362; S-38 to L-362; Q-39 to L-362; F-40 to L-362; S-41 to L-362; D-42 to L-362; K-43 to L-362; P-44 to L-362; V-45 to L-362; Q-46 to L-362; D-47 to L-362; R-48 to L-362; G-49 to L-362; L-50 to L-362; V-51 to L-362; V-52 to L-362; T-53 to L-362; D-54 to L-362; L-55 to L-362; K-56 to L-362; A-57 to L-362; E-58 to
25 L-362; S-59 to L-362; V-60 to L-362; V-61 to L-362; L-62 to L-362; E-63 to L-362; H-64 to L-362; R-65 to L-362; S-66 to L-362; Y-67 to L-362; C-68 to L-362; S-69 to L-362; A-70 to L-362; K-71 to L-362; A-72 to L-362; R-73 to L-362; D-74 to L-362; R-75 to L-362; H-76 to L-362; F-77 to L-362; A-78 to L-362; G-79 to L-362; D-80 to L-362; V-81 to L-362; L-82 to L-362; G-83 to L-362; Y-84 to L-362; V-85 to L-362;
30 T-86 to L-362; P-87 to L-362; W-88 to L-362; N-89 to L-362; S-90 to L-362; H-91 to L-362; G-92 to L-362; Y-93 to L-362; D-94 to L-362; V-95 to L-362; T-96 to L-362; K-97 to L-362; V-98 to L-362; F-99 to L-362; G-100 to L-362; S-101 to L-362; K-

102 to L-362; F-103 to L-362; T-104 to L-362; Q-105 to L-362; I-106 to L-362; S-
107 to L-362; P-108 to L-362; V-109 to L-362; W-110 to L-362; L-111 to L-362; Q-
112 to L-362; L-113 to L-362; K-114 to L-362; R-115 to L-362; R-116 to L-362; G-
117 to L-362; R-118 to L-362; E-119 to L-362; M-120 to L-362; F-121 to L-362; E-
5 122 to L-362; V-123 to L-362; T-124 to L-362; G-125 to L-362; L-126 to L-362; H-
127 to L-362; D-128 to L-362; V-129 to L-362; D-130 to L-362; Q-131 to L-362; G-
132 to L-362; W-133 to L-362; M-134 to L-362; R-135 to L-362; A-136 to L-362; V-
137 to L-362; R-138 to L-362; K-139 to L-362; H-140 to L-362; A-141 to L-362; K-
142 to L-362; G-143 to L-362; L-144 to L-362; H-145 to L-362; I-146 to L-362; V-
10 147 to L-362; P-148 to L-362; R-149 to L-362; L-150 to L-362; L-151 to L-362; F-
152 to L-362; E-153 to L-362; D-154 to L-362; W-155 to L-362; T-156 to L-362; Y-
157 to L-362; D-158 to L-362; D-159 to L-362; F-160 to L-362; R-161 to L-362; N-
162 to L-362; V-163 to L-362; L-164 to L-362; D-165 to L-362; S-166 to L-362; E-
167 to L-362; D-168 to L-362; E-169 to L-362; I-170 to L-362; E-171 to L-362; E-
15 172 to L-362; L-173 to L-362; S-174 to L-362; K-175 to L-362; T-176 to L-362; V-
177 to L-362; V-178 to L-362; Q-179 to L-362; V-180 to L-362; A-181 to L-362; K-
182 to L-362; N-183 to L-362; Q-184 to L-362; H-185 to L-362; F-186 to L-362; D-
187 to L-362; G-188 to L-362; F-189 to L-362; V-190 to L-362; V-191 to L-362; E-
192 to L-362; V-193 to L-362; W-194 to L-362; N-195 to L-362; Q-196 to L-362; L-
20 197 to L-362; L-198 to L-362; S-199 to L-362; Q-200 to L-362; K-201 to L-362; R-
202 to L-362; V-203 to L-362; T-204 to L-362; D-205 to L-362; Q-206 to L-362; L-
207 to L-362; G-208 to L-362; M-209 to L-362; F-210 to L-362; T-211 to L-362; H-
212 to L-362; K-213 to L-362; E-214 to L-362; F-215 to L-362; E-216 to L-362; Q-
217 to L-362; L-218 to L-362; A-219 to L-362; P-220 to L-362; V-221 to L-362; L-
25 222 to L-362; D-223 to L-362; G-224 to L-362; F-225 to L-362; S-226 to L-362; L-
227 to L-362; M-228 to L-362; T-229 to L-362; Y-230 to L-362; D-231 to L-362; Y-
232 to L-362; S-233 to L-362; T-234 to L-362; A-235 to L-362; H-236 to L-362; Q-
237 to L-362; P-238 to L-362; G-239 to L-362; P-240 to L-362; N-241 to L-362; A-
242 to L-362; P-243 to L-362; L-244 to L-362; S-245 to L-362; W-246 to L-362; V-
30 247 to L-362; R-248 to L-362; A-249 to L-362; C-250 to L-362; V-251 to L-362; Q-
252 to L-362; V-253 to L-362; L-254 to L-362; D-255 to L-362; P-256 to L-362; K-
257 to L-362; S-258 to L-362; K-259 to L-362; W-260 to L-362; R-261 to L-362; S-

262 to L-362; K-263 to L-362; I-264 to L-362; L-265 to L-362; L-266 to L-362; G-267 to L-362; L-268 to L-362; N-269 to L-362; F-270 to L-362; Y-271 to L-362; G-272 to L-362; M-273 to L-362; D-274 to L-362; Y-275 to L-362; A-276 to L-362; T-277 to L-362; S-278 to L-362; K-279 to L-362; D-280 to L-362; A-281 to L-362; R-282 to L-362; E-283 to L-362; P-284 to L-362; V-285 to L-362; V-286 to L-362; G-287 to L-362; A-288 to L-362; R-289 to L-362; Y-290 to L-362; I-291 to L-362; Q-292 to L-362; T-293 to L-362; L-294 to L-362; K-295 to L-362; D-296 to L-362; H-297 to L-362; R-298 to L-362; P-299 to L-362; R-300 to L-362; M-301 to L-362; V-302 to L-362; W-303 to L-362; D-304 to L-362; S-305 to L-362; Q-306 to L-362; X-307 to L-362; S-308 to L-362; E-309 to L-362; H-310 to L-362; F-311 to L-362; F-312 to L-362; E-313 to L-362; Y-314 to L-362; K-315 to L-362; K-316 to L-362; S-317 to L-362; R-318 to L-362; S-319 to L-362; G-320 to L-362; R-321 to L-362; H-322 to L-362; V-323 to L-362; V-324 to L-362; F-325 to L-362; Y-326 to L-362; P-327 to L-362; T-328 to L-362; L-329 to L-362; K-330 to L-362; S-331 to L-362; L-332 to L-362; Q-333 to L-362; V-334 to L-362; R-335 to L-362; L-336 to L-362; E-337 to L-362; L-338 to L-362; A-339 to L-362; R-340 to L-362; E-341 to L-362; L-342 to L-362; G-343 to L-362; V-344 to L-362; G-345 to L-362; V-346 to L-362; S-347 to L-362; I-348 to L-362; W-349 to L-362; E-350 to L-362; L-351 to L-362; G-352 to L-362; Q-353 to L-362; G-354 to L-362; L-355 to L-362; D-356 to L-362; and Y-357 to L-362 of SEQ ID NO:278. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: R-2 to H-307; T-3 to H-307; L-4 to H-307; F-5 to H-307; N-6 to H-307; L-7 to H-307; L-8 to H-307; W-9 to H-307; L-10 to H-307; A-11 to H-307; L-12 to H-307; A-13 to H-307; C-14 to H-307; S-15 to H-307; P-16 to H-307; V-17 to H-307; H-18 to H-307; T-19 to H-307; T-20 to H-307; L-21 to H-307; S-22 to H-307; K-23 to H-307; S-24 to H-307; D-25 to H-307; A-26 to H-307; K-27 to H-307; K-28 to H-307; A-29 to H-307; A-30 to H-307; S-31 to H-307; K-32 to H-307; T-33 to H-307; L-34 to H-307; L-35 to H-307; E-36 to H-307; K-37 to H-307; S-38 to H-307; Q-39 to H-307; F-40 to H-307; S-41 to H-307; D-42 to H-307; K-43 to H-307; P-44 to H-307; V-45 to H-307; Q-46 to H-307; D-47 to H-307; R-48 to H-307; G-49 to H-307;

L-50 to H-307; V-51 to H-307; V-52 to H-307; T-53 to H-307; D-54 to H-307; L-55 to H-307; K-56 to H-307; A-57 to H-307; E-58 to H-307; S-59 to H-307; V-60 to H-307; V-61 to H-307; L-62 to H-307; E-63 to H-307; H-64 to H-307; R-65 to H-307; S-66 to H-307; Y-67 to H-307; C-68 to H-307; S-69 to H-307; A-70 to H-307; K-71 to H-307; A-72 to H-307; R-73 to H-307; D-74 to H-307; R-75 to H-307; H-76 to H-307; F-77 to H-307; A-78 to H-307; G-79 to H-307; D-80 to H-307; V-81 to H-307; L-82 to H-307; G-83 to H-307; Y-84 to H-307; V-85 to H-307; T-86 to H-307; P-87 to H-307; W-88 to H-307; N-89 to H-307; S-90 to H-307; H-91 to H-307; G-92 to H-307; Y-93 to H-307; D-94 to H-307; V-95 to H-307; T-96 to H-307; K-97 to H-307; V-98 to H-307; F-99 to H-307; G-100 to H-307; S-101 to H-307; K-102 to H-307; F-103 to H-307; T-104 to H-307; Q-105 to H-307; I-106 to H-307; S-107 to H-307; P-108 to H-307; V-109 to H-307; W-110 to H-307; L-111 to H-307; Q-112 to H-307; L-113 to H-307; K-114 to H-307; R-115 to H-307; R-116 to H-307; G-117 to H-307; R-118 to H-307; E-119 to H-307; M-120 to H-307; F-121 to H-307; E-122 to H-307; V-123 to H-307; T-124 to H-307; G-125 to H-307; L-126 to H-307; H-127 to H-307; D-128 to H-307; V-129 to H-307; D-130 to H-307; Q-131 to H-307; G-132 to H-307; W-133 to H-307; M-134 to H-307; R-135 to H-307; A-136 to H-307; V-137 to H-307; R-138 to H-307; K-139 to H-307; H-140 to H-307; A-141 to H-307; K-142 to H-307; G-143 to H-307; L-144 to H-307; H-145 to H-307; I-146 to H-307; V-147 to H-307; P-148 to H-307; R-149 to H-307; L-150 to H-307; L-151 to H-307; F-152 to H-307; E-153 to H-307; D-154 to H-307; W-155 to H-307; T-156 to H-307; Y-157 to H-307; D-158 to H-307; D-159 to H-307; F-160 to H-307; R-161 to H-307; N-162 to H-307; V-163 to H-307; L-164 to H-307; D-165 to H-307; S-166 to H-307; E-167 to H-307; D-168 to H-307; E-169 to H-307; I-170 to H-307; E-171 to H-307; E-172 to H-307; L-173 to H-307; S-174 to H-307; K-175 to H-307; T-176 to H-307; V-177 to H-307; V-178 to H-307; Q-179 to H-307; V-180 to H-307; A-181 to H-307; K-182 to H-307; N-183 to H-307; Q-184 to H-307; H-185 to H-307; F-186 to H-307; D-187 to H-307; G-188 to H-307; F-189 to H-307; V-190 to H-307; V-191 to H-307; E-192 to H-307; V-193 to H-307; W-194 to H-307; N-195 to H-307; Q-196 to H-307; L-197 to H-307; L-198 to H-307; S-199 to H-307; Q-200 to H-307; K-201 to H-307; R-202 to H-307; V-203 to H-307; G-204 to H-307; L-205 to H-307; I-206 to H-307; H-207 to H-307; M-208 to H-307; L-209 to H-307; T-210 to H-307; H-211 to H-307; L-212 to

H-307; A-213 to H-307; E-214 to H-307; A-215 to H-307; L-216 to H-307; H-217 to H-307; Q-218 to H-307; A-219 to H-307; R-220 to H-307; L-221 to H-307; L-222 to H-307; A-223 to H-307; L-224 to H-307; L-225 to H-307; V-226 to H-307; I-227 to H-307; P-228 to H-307; P-229 to H-307; A-230 to H-307; I-231 to H-307; T-232 to H-307; P-233 to H-307; G-234 to H-307; T-235 to H-307; D-236 to H-307; Q-237 to H-307; L-238 to H-307; G-239 to H-307; M-240 to H-307; F-241 to H-307; T-242 to H-307; H-243 to H-307; K-244 to H-307; E-245 to H-307; F-246 to H-307; E-247 to H-307; Q-248 to H-307; L-249 to H-307; A-250 to H-307; P-251 to H-307; V-252 to H-307; L-253 to H-307; D-254 to H-307; G-255 to H-307; F-256 to H-307; S-257 to H-307; L-258 to H-307; M-259 to H-307; T-260 to H-307; Y-261 to H-307; D-262 to H-307; Y-263 to H-307; S-264 to H-307; T-265 to H-307; A-266 to H-307; H-267 to H-307; Q-268 to H-307; P-269 to H-307; G-270 to H-307; P-271 to H-307; N-272 to H-307; A-273 to H-307; P-274 to H-307; L-275 to H-307; S-276 to H-307; W-277 to H-307; V-278 to H-307; R-279 to H-307; A-280 to H-307; C-281 to H-307; V-282 to H-307; Q-283 to H-307; V-284 to H-307; L-285 to H-307; D-286 to H-307; P-287 to H-307; K-288 to H-307; S-289 to H-307; K-290 to H-307; W-291 to H-307; R-292 to H-307; S-293 to H-307; K-294 to H-307; I-295 to H-307; L-296 to H-307; L-297 to H-307; G-298 to H-307; L-299 to H-307; N-300 to H-307; F-301 to H-307; and Y-302 to H-307 of SEQ ID NO: 1232. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand, ability to generate antibodies, ability to bind antibodies) may still be retained. For example the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a

large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one
5 or more residues deleted from the carboxyl terminus of the amino acid sequence of the polypeptide shown in Figures 1A-B (SEQ ID NO:278), as described by the general formula 1-n, where n is an integer from 6 to 356, where n corresponds to the position of the amino acid residue identified in SEQ ID NO:278. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or
10 alternatively consisting of, an amino acid sequence selected from the group: K-23 to L-362; K-23 to L-361; K-23 to D-360; K-23 to Y-359; K-23 to F-358; K-23 to Y-357; K-23 to D-356; K-23 to L-355; K-23 to G-354; K-23 to Q-353; K-23 to G-352; K-23 to L-351; K-23 to E-350; K-23 to W-349; K-23 to I-348; K-23 to S-347; K-23 to V-346; K-23 to G-345; K-23 to V-344; K-23 to G-343; K-23 to L-342; K-23 to E-341;
15 K-23 to R-340; K-23 to A-339; K-23 to L-338; K-23 to E-337; K-23 to L-336; K-23 to R-335; K-23 to V-334; K-23 to Q-333; K-23 to L-332; K-23 to S-331; K-23 to K-330; K-23 to L-329; K-23 to T-328; K-23 to P-327; K-23 to Y-326; K-23 to F-325; K-23 to V-324; K-23 to V-323; K-23 to H-322; K-23 to R-321; K-23 to G-320; K-23 to S-319; K-23 to R-318; K-23 to S-317; K-23 to K-316; K-23 to K-315; K-23 to Y-314; K-23 to E-313; K-23 to F-312; K-23 to F-311; K-23 to H-310; K-23 to E-309; K-23 to S-308; K-23 to X-307; K-23 to Q-306; K-23 to S-305; K-23 to D-304; K-23 to W-303; K-23 to V-302; K-23 to M-301; K-23 to R-300; K-23 to P-299; K-23 to R-298; K-23 to H-297; K-23 to D-296; K-23 to K-295; K-23 to L-294; K-23 to T-293; K-23 to Q-292; K-23 to I-291; K-23 to Y-290; K-23 to R-289; K-23 to A-288; K-23
25 to G-287; K-23 to V-286; K-23 to V-285; K-23 to P-284; K-23 to E-283; K-23 to R-282; K-23 to A-281; K-23 to D-280; K-23 to K-279; K-23 to S-278; K-23 to T-277; K-23 to A-276; K-23 to Y-275; K-23 to D-274; K-23 to M-273; K-23 to G-272; K-23 to Y-271; K-23 to F-270; K-23 to N-269; K-23 to L-268; K-23 to G-267; K-23 to L-266; K-23 to L-265; K-23 to I-264; K-23 to K-263; K-23 to S-262; K-23 to R-261; K-23
30 to W-260; K-23 to K-259; K-23 to S-258; K-23 to K-257; K-23 to P-256; K-23 to D-255; K-23 to L-254; K-23 to V-253; K-23 to Q-252; K-23 to V-251; K-23 to C-250; K-23 to A-249; K-23 to R-248; K-23 to V-247; K-23 to W-246; K-23 to S-245;

K-23 to L-244; K-23 to P-243; K-23 to A-242; K-23 to N-241; K-23 to P-240; K-23 to G-239; K-23 to P-238; K-23 to Q-237; K-23 to H-236; K-23 to A-235; K-23 to T-234; K-23 to S-233; K-23 to Y-232; K-23 to D-231; K-23 to Y-230; K-23 to T-229; K-23 to M-228; K-23 to L-227; K-23 to S-226; K-23 to F-225; K-23 to G-224; K-23 to D-223; K-23 to L-222; K-23 to V-221; K-23 to P-220; K-23 to A-219; K-23 to L-218; K-23 to Q-217; K-23 to E-216; K-23 to F-215; K-23 to E-214; K-23 to K-213; K-23 to H-212; K-23 to T-211; K-23 to F-210; K-23 to M-209; K-23 to G-208; K-23 to L-207; K-23 to Q-206; K-23 to D-205; K-23 to T-204; K-23 to V-203; K-23 to R-202; K-23 to K-201; K-23 to Q-200; K-23 to S-199; K-23 to L-198; K-23 to L-197; K-23 to Q-196; K-23 to N-195; K-23 to W-194; K-23 to V-193; K-23 to E-192; K-23 to V-191; K-23 to V-190; K-23 to F-189; K-23 to G-188; K-23 to D-187; K-23 to F-186; K-23 to H-185; K-23 to Q-184; K-23 to N-183; K-23 to K-182; K-23 to A-181; K-23 to V-180; K-23 to Q-179; K-23 to V-178; K-23 to V-177; K-23 to T-176; K-23 to K-175; K-23 to S-174; K-23 to L-173; K-23 to E-172; K-23 to E-171; K-23 to I-170; K-23 to E-169; K-23 to D-168; K-23 to E-167; K-23 to S-166; K-23 to D-165; K-23 to L-164; K-23 to V-163; K-23 to N-162; K-23 to R-161; K-23 to F-160; K-23 to D-159; K-23 to D-158; K-23 to Y-157; K-23 to T-156; K-23 to W-155; K-23 to D-154; K-23 to E-153; K-23 to F-152; K-23 to L-151; K-23 to L-150; K-23 to R-149; K-23 to P-148; K-23 to V-147; K-23 to I-146; K-23 to H-145; K-23 to L-144; K-23 to G-143; K-23 to K-142; K-23 to A-141; K-23 to H-140; K-23 to K-139; K-23 to R-138; K-23 to V-137; K-23 to A-136; K-23 to R-135; K-23 to M-134; K-23 to W-133; K-23 to G-132; K-23 to Q-131; K-23 to D-130; K-23 to V-129; K-23 to D-128; K-23 to H-127; K-23 to L-126; K-23 to G-125; K-23 to T-124; K-23 to V-123; K-23 to E-122; K-23 to F-121; K-23 to M-120; K-23 to E-119; K-23 to R-118; K-23 to G-117; K-23 to R-116; K-23 to R-115; K-23 to K-114; K-23 to L-113; K-23 to Q-112; K-23 to L-111; K-23 to W-110; K-23 to V-109; K-23 to P-108; K-23 to S-107; K-23 to I-106; K-23 to Q-105; K-23 to T-104; K-23 to F-103; K-23 to K-102; K-23 to S-101; K-23 to G-100; K-23 to F-99; K-23 to V-98; K-23 to K-97; K-23 to T-96; K-23 to V-95; K-23 to D-94; K-23 to Y-93; K-23 to G-92; K-23 to H-91; K-23 to S-90; K-23 to N-89; K-23 to W-88; K-23 to P-87; K-23 to T-86; K-23 to V-85; K-23 to Y-84; K-23 to G-83; K-23 to L-82; K-23 to V-81; K-23 to D-80; K-23 to G-79; K-23 to A-78; K-23 to F-77; K-23 to H-76; K-23 to R-75; K-23 to D-74; K-23 to R-73; K-23 to A-72;

K-23 to K-71; K-23 to A-70; K-23 to S-69; K-23 to C-68; K-23 to Y-67; K-23 to S-66; K-23 to R-65; K-23 to H-64; K-23 to E-63; K-23 to L-62; K-23 to V-61; K-23 to V-60; K-23 to S-59; K-23 to E-58; K-23 to A-57; K-23 to K-56; K-23 to L-55; K-23 to D-54; K-23 to T-53; K-23 to V-52; K-23 to V-51; K-23 to L-50; K-23 to G-49; K-23 to R-48; K-23 to D-47; K-23 to Q-46; K-23 to V-45; K-23 to P-44; K-23 to K-43; K-23 to D-42; K-23 to S-41; K-23 to F-40; K-23 to Q-39; K-23 to S-38; K-23 to K-37; K-23 to E-36; K-23 to L-35; K-23 to L-34; K-23 to T-33; K-23 to K-32; K-23 to S-31; K-23 to A-30; and K-23 to A-29 of SEQ ID NO:278. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

10 Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: K-23 to R-306; K-23 to S-305; K-23 to T-304; K-23 to G-303; K-23 to Y-302; K-23 to F-301; K-23 to N-300; K-23 to L-299; K-23 to G-298; K-23 to L-297; K-23 to L-296; K-23 to I-295; K-23 to K-294; K-23 to S-293; K-23 to R-292; K-23 to W-291; K-23 to K-290; K-23 to S-289; K-23 to K-288; K-23 to P-287; K-23 to D-286; K-23 to L-285; K-23 to V-284; K-23 to Q-283; K-23 to V-282; K-23 to C-281; K-23 to A-280; K-23 to R-279; K-23 to V-278; K-23 to W-277; K-23 to S-276; K-23 to L-275; K-23 to P-274; K-23 to A-273; K-23 to N-272; K-23 to P-271; K-23 to G-270; K-23 to P-269; K-23 to Q-268; K-23 to H-267; K-23 to A-266; K-23 to T-265; K-23 to S-264; K-23 to Y-263; K-23 to D-262; K-23 to Y-261; K-23 to T-260; K-23 to M-259; K-23 to L-258; K-23 to S-257; K-23 to F-256; K-23 to G-255; K-23 to D-254; K-23 to L-253; K-23 to V-252; K-23 to P-251; K-23 to A-250; K-23 to L-249; K-23 to Q-248; K-23 to E-247; K-23 to F-246; K-23 to E-245; K-23 to K-244; K-23 to H-243; K-23 to T-242; K-23 to F-241; K-23 to M-240; K-23 to G-239; K-23 to L-238; K-23 to Q-237; K-23 to D-236; K-23 to T-235; K-23 to G-234; K-23 to P-233; K-23 to T-232; K-23 to I-231; K-23 to A-230; K-23 to P-229; K-23 to P-228; K-23 to I-227; K-23 to V-226; K-23 to L-225; K-23 to L-224; K-23 to A-223; K-23 to L-222; K-23 to L-221; K-23 to R-220; K-23 to A-219; K-23 to Q-218; K-23 to H-217; K-23 to L-216; K-23 to A-215; K-23 to E-214; K-23 to A-213; K-23 to L-212; K-23 to H-211; K-23 to T-210; K-23 to L-209; K-23 to M-208; K-23 to H-207; K-23 to I-206; K-23 to L-205; K-23 to G-204; K-23 to V-203; K-23 to R-202; K-23 to K-201; K-23 to Q-200; K-23 to S-199; K-23 to L-198; K-23 to L-197; K-23 to Q-196; K-23 to N-

195; K-23 to W-194; K-23 to V-193; K-23 to E-192; K-23 to V-191; K-23 to V-190; K-23 to F-189; K-23 to G-188; K-23 to D-187; K-23 to F-186; K-23 to H-185; K-23 to Q-184; K-23 to N-183; K-23 to K-182; K-23 to A-181; K-23 to V-180; K-23 to Q-179; K-23 to V-178; K-23 to V-177; K-23 to T-176; K-23 to K-175; K-23 to S-174;
5 K-23 to L-173; K-23 to E-172; K-23 to E-171; K-23 to I-170; K-23 to E-169; K-23 to D-168; K-23 to E-167; K-23 to S-166; K-23 to D-165; K-23 to L-164; K-23 to V-163; K-23 to N-162; K-23 to R-161; K-23 to F-160; K-23 to D-159; K-23 to D-158; K-23 to Y-157; K-23 to T-156; K-23 to W-155; K-23 to D-154; K-23 to E-153; K-23 to F-152; K-23 to L-151; K-23 to L-150; K-23 to R-149; K-23 to P-148; K-23 to V-147;
10 K-23 to I-146; K-23 to H-145; K-23 to L-144; K-23 to G-143; K-23 to K-142; K-23 to A-141; K-23 to H-140; K-23 to K-139; K-23 to R-138; K-23 to V-137; K-23 to A-136; K-23 to R-135; K-23 to M-134; K-23 to W-133; K-23 to G-132; K-23 to Q-131; K-23 to D-130; K-23 to V-129; K-23 to D-128; K-23 to H-127; K-23 to L-126; K-23 to G-125; K-23 to T-124; K-23 to V-123; K-23 to E-122; K-23 to F-121; K-23 to M-120; K-23 to E-119; K-23 to R-118; K-23 to G-117; K-23 to R-116; K-23 to R-115; K-23 to K-114; K-23 to L-113; K-23 to Q-112; K-23 to L-111; K-23 to W-110; K-23 to V-109; K-23 to P-108; K-23 to S-107; K-23 to I-106; K-23 to Q-105; K-23 to T-104; K-23 to F-103; K-23 to K-102; K-23 to S-101; K-23 to G-100; K-23 to F-99; K-23 to V-98; K-23 to K-97; K-23 to T-96; K-23 to V-95; K-23 to D-94; K-23 to Y-93;
20 K-23 to G-92; K-23 to H-91; K-23 to S-90; K-23 to N-89; K-23 to W-88; K-23 to P-87; K-23 to T-86; K-23 to V-85; K-23 to Y-84; K-23 to G-83; K-23 to L-82; K-23 to V-81; K-23 to D-80; K-23 to G-79; K-23 to A-78; K-23 to F-77; K-23 to H-76; K-23 to R-75; K-23 to D-74; K-23 to R-73; K-23 to A-72; K-23 to K-71; K-23 to A-70; K-23 to S-69; K-23 to C-68; K-23 to Y-67; K-23 to S-66; K-23 to R-65; K-23 to H-64;
25 K-23 to E-63; K-23 to L-62; K-23 to V-61; K-23 to V-60; K-23 to S-59; K-23 to E-58; K-23 to A-57; K-23 to K-56; K-23 to L-55; K-23 to D-54; K-23 to T-53; K-23 to V-52; K-23 to V-51; K-23 to L-50; K-23 to G-49; K-23 to R-48; K-23 to D-47; K-23 to Q-46; K-23 to V-45; K-23 to P-44; K-23 to K-43; K-23 to D-42; K-23 to S-41; K-23 to F-40; K-23 to Q-39; K-23 to S-38; K-23 to K-37; K-23 to E-36; K-23 to L-35;
30 K-23 to L-34; K-23 to T-33; K-23 to K-32; K-23 to S-31; K-23 to A-30; and K-23 to A-29 of SEQ ID NO:1232. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:278, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209080, where this portion excludes any integer of amino acid residues from 1 to about 356 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209080, or any integer of amino acid residues from 1 to about 356 amino acids from the carboxyl terminus, or any combination of the above amino terminal and carboxyl terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209080. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention have uses, such as, for example, as a marker in linkage analysis for chromosome 11.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, immune and gastrointestinal disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

When tested against Jurkat cell lines, supernatants removed from cells expressing this gene activated the nuclear-factor kB (NF-kB) transcription factor. Thus, it is likely that this gene activates Jurkat cells by activating a transcriptional factor found within these cells. Nuclear factor kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element were used to screen supernatants for such activity.

Additionally, products of this gene have been found to inhibit the Mixed Lymphocyte Reaction (MLR). This assay is described in Example 58 herein. Inhibition of a MLR may be due to a direct effect on cell proliferation and viability; modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

The tissue distribution in immune cells (e.g., T-cells, macrophages) and inhibition of the MLR indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of many diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus

erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore, polynucleotides and polypeptides of the invention (including fragments, variants, and derivatives) may be also used to treat, prevent and/or diagnose immunological disorders including, but not limited to, arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma.

The tissue distribution in human T-cells and human colon carcinoma indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of immune disorders and gastrointestinal diseases. Non-limiting representative uses for these polynucleotides and polypeptides are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may as be useful as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, in the differentiation and/or proliferation of various cell types (e.g., T, B and natural killer lymphocytes, monocytes, dendritic cells), modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, and/or modulation of cytokine production by accessory cells.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1501 of SEQ ID NO:40, b is an integer of 15 to 1515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene shares sequence homology with Ribosomal protein L11 of *Caenorhabditis elegans*. (See Genbank Accession No. 156201.)

20 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
 ERGVSINQFCKEFNERTKDIKEGIPLPTKILVKPDRTFEIKIGQPTVSYFLKAAA
 GI EKGARQTGKEVAGLVTLKHVYEIARIKAQDEAFALQDVPLSSVVRSIIG
 SARSLGIRVVKDLSSEELAAF QKERAIFLAAQKEADLAAQEAAKK (SEQ ID
 25 NO:564), ERGVSINQFCKEFNERTKDIKEGIPLPTKILVKPDRTFEIKIGQ
 PTVSYFL (SEQ ID NO:565), KAAAGIEKGARQTGKEVAGLVTLKHVYEIARIK
 AQDEAFALQDVPLSSV (SEQ ID NO:566), and/or VRSIIGSARSLGIRVVK
 DLSSEELAAFQKERAIFLAAQKEADLAAQEAAKK (SEQ ID NO:567).

30 Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed in human embryo tissue, and to a lesser extent, in human epithelioid sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, development disorders and epithelial cell cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the embryonic and epithelial cell systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. embryonic, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 279 as residues: Lys-34 to Gly-40.

The tissue distribution in human embryo indicates that the protein product of this gene is useful for the diagnosis and treatment of developmental disorders and epithelial cancer. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 690 of SEQ ID NO:41, b is an integer of 15 to 704, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 32

This gene is expressed primarily in resting T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory and general immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that the protein product of this gene is useful for the diagnosis and treatment of disorders of the immune system.

Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as,
5 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:42, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

This gene is believed to reside on chromosome 1. Accordingly, polynucleotides derived from this gene are useful in linkage analysis as chromosome
25 1 markers.

This gene is expressed primarily in prostate, and to a lesser extent in soares adult brain, human umbilical vein endothelial cells, and amniotic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
30 and for diagnosis of diseases and conditions which include, but are not limited to, prostate-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary system and nervous system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate indicates that the protein products of this gene are useful for the diagnosis and treatment of disorders of the urinary and nervous systems. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1807 of SEQ ID NO:43, b is an integer of 15 to 1821, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene shares sequence homology with R05G6.4 gene product. (See Genbank Accession No. gi|1326338.) This gene also shares sequence homology with the cyclophilin-like protein CyP-60. (See Genbank Accession No. 1199598, see also Biochem. J. 314 (1), 313-319 (1996).)

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- AVYTYHEKKKDDTAASGYGTQNIRLSRDAVKDFDCCCLSLQPCHDPVVTPDG
 YLYEREAILEYILHQKKEIARQMKAIEKQRGTRREEQKELQRAASQDHVRGF
 LEKESAIIVSRPLNPFTAKALSGTSPDDVQPGPSVGPPSKDKDKVLPSFWIPSLT
 10 PEAKATKLEKPSRTVTCMSGKPLRMSDLTPVHFTPLDSSVDRVGLITRSERY
 VCAVTRDSLSNATPCAVLRPSGAVVTLECVKLIIRKDMVDPVTGDKLTDRDII
 VLQRRGGT (SEQ ID NO:568),
 YLYEREAILEYILHQKKEIARQMKAIEKQRGTRREEQKELQRAASQDHVRGF
 LE (SEQ ID NO:569),
 15 FTAKALSGTSPDDVQPGPSVGPPSKDKDKVLPSFWIPSLTPEAKATKLEKPSR
 TVTCMSGKPL (SEQ ID NO:570),
 VHFTPLDSSVDRVGLITRSERYVCAVTRDSLSNATPCAVLRPSGAVVTLECVK
 LI (SEQ ID NO:571), and/or
 MSDLTPVHFTPLDSSVDRVGLITRSERYVCAVTRDSLSNATPCAVLRPSGAVV
 20 TLECVKLIIRKDM (SEQ ID NO:572).

- Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 25 encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human testis, and to a lesser extent in activated T-cells.

- 30 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

male reproductive disorders and in particular testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the

5 reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression

10 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human testis indicates that the protein product of this gene is useful for the diagnosis and treatment of disorders of the male reproductive system, and in particular of testicular cancer. Furthermore, this gene is useful for the

15 treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is

20 believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone

25 formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

30 related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1010 of SEQ ID NO:44, b is an integer of 15 to 1024, where both a and b correspond to the positions of nucleotide
5 residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

10 The translation product of this gene shares sequence homology with Lpe5p of *Saccharomyces cerevisiae*, which is thought to be important in the metabolism of phospholipids. The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

15 This gene is expressed primarily in liver and brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders. Similarly, polypeptides and antibodies directed to these
20 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic and nervous systems expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. liver, brain, cancerous and wounded tissues) or bodily fluids
25 (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
30 NO: 283 as residues: Pro-14 to Leu-20, Lys-28 to Asn-38, Arg-109 to Arg-114, Lys-119 to Asn-124, Glu-152 to Leu-157, or Pro-172 to Val-180.

The tissue distribution in liver and brain, combined with the homology to Lpe5p of *Saccharomyces cerevisiae* indicates that the protein product of this gene is useful for the diagnosis and treatment of metabolic and nervous disorders.

Additionally, the tissue distribution indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 969 of SEQ ID NO:45, b is an integer of 15 to 983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene shares sequence homology with the nuclear ribonucleoprotein U (HNRNP U), encoded by *C. elegans* (See Genbank Accession gi|1703576.).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MDTSENRPENDVPEPPMPIADQVSNDDRPEGSVEDEEKKESSLPKSFKRKISV
VSATKGVPAAGNSDTEGGQPGRKRRWGASTATTQKKPSISITTESLKSLIPDIKP
LAGQEAVVDLHADDSETERNGDDGTHDKGLKICRTVTQVVPVPAEGQE
NGQREEEEEKEPEAEPPVPPQVSVEVALPPPAEHEVKVTLGDTLTRRSISQ
QKSGVSITIDDPVRTAQVPSPPRGKISNIVHISNLVRPFTLGQLKELLGRTGTLV

EEAFWIDKIKSHCFVTYSTVEEAVATRTALHGVKWPQSNPKFLCADYAEQDE
 LDYHRGLLVDRPSETKTEEQGIPRPLHPPPPPVQPPQHPRAEQREQERAVRE
 QWAEREREMERRERTRSEREWDRDKV VREGPRSRSRSRXRRRKERAKSKEK
 KSEKKEKAQEPPAKLLDDLFRKTKAAPCIYWLPLTDSQIVQKEAERAERAK
 5 EREKRRKEQEEEEQKEREKEAERERNRQLEREKRREHSRERDRERERERERD
 RGDRDRDRERDRERGRERDRRDTKRHSRSRSRSTPVRDRGGR (SEQ ID
 NO:573),
 ENDVPEPPMPIADQVSNDDRPEGSVEDEEKKESLPKSFKRKISVVSA (SEQ ID
 NO:574), VDLHADDRISEDETERNGDDGTHDKGLKICRTVTQV (SEQ ID
 10 NO:575),
 PQVSVEVALPPPAEHEVKKVTLGDTLTRRSISQQKSGVSITIDDPVRTAQVPSP
 P (SEQ ID NO:576),
 LKELLGRTGTLVEEAFWIDKIKSHCFVTYSTVEEAVATRTALHGVKWPQSNP
 KFL (SEQ ID NO:577),
 15 VDRPSETKTEEQGIPRPLHPPPPPVQPPQHPRAEQREQERAVREQWAERERE
 (SEQ ID NO:578),
 EWDRDKVREGPRSRSRSRXRRRKERAKSKEKKSEKKEKAQEPPAKLLDDLFR
 RKTKAAP (SEQ ID NO:579), LDVPLASRSPEFPLPLMTQSELPRCPPHPGAR
 (SEQ ID NO:581), LATLSISPIWSVLSL (SEQ ID NO:582), and
 20 PLTDSQIVQKEAERAERAKEREKRRKEQEEEEQKEREKEAERERNRQLEREK
 RREHSRERDRER (SEQ ID NO:580). Moreover, fragments and variants of these
 polypeptides (such as, for example, fragments as described herein, polypeptides at
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent
 25 conditions, to the polynucleotide encoding these polypeptides) are encompassed by
 the invention. Antibodies that bind polypeptides of the invention are also
 encompassed by the invention. Polynucleotides encoding these polypeptides are also
 encompassed by the invention.

An additional embodiment is the polynucleotides encoding these polypeptides.

30 The gene encoding the disclosed cDNA is thought to reside on chromosome 14.
 Accordingly, polynucleotides related to this invention are useful as a marker in
 linkage analysis for chromosome 14.

This gene is expressed primarily in epididymus, and to a lesser extent in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the male reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. epididymus, testes, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in epididymus and testes indicates that the protein product of this gene is useful for the diagnosis and treatment of male reproductive disorders. Furthermore, the protein product of this gene is useful for the treatment and diagnosis of conditions concerning proper reproductive and testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

This gene is expressed primarily in amygdala.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory diseases and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the amygdala, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in amygdala indicates that the protein product of this gene is useful for the diagnosis and treatment of inflammatory diseases and neural disorders. The amygdala processes sensory information and relays this to other areas of the brain including the endocrine and autonomic domains of the hypothalamus and the brain stem. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 826 of SEQ ID NO:47, b is an integer of 15 to 840, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

This gene shares sequence homology with human opsonin protein P35
 5 fragment. (See Genbank Accession No. R94181.) The opsonin protein activates the
 phagocytosis of pathogenic microbes by phagocytic cells which indicates that the
 protein product of this gene may be useful in the treatment and/or prevention of a
 variety of immune conditions, particularly bacterial infections and antigen
 presentation.

10 In specific embodiments, polypeptides of the invention comprise, or
 alternatively consists of, an amino acid sequence selected from the group:
 GCDSCPHLPREAFAQDTQAEGECSSRAERADMCPDAPPSQEVPEGPGAAP
 (SEQ ID NO:583),
 RGWLPSSCLSCALRVCPDSSSTQAMGMLLAFWLPGASWQEAARGQYSEDED
 15 TDTDEYKEAKASINPVTGRVVEEKPPNPMEGMTEEQKEHEA (SEQ ID NO:584),
 and/or TQAMGMLLAFWLPGASWQEAARGQYSE (SEQ ID NO:585). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 20 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

This gene is expressed in immune-related tissues such as thymus, macrophage,
 25 and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 immune disorders and infectious diseases. Similarly, polypeptides and antibodies
 30 directed to these polypeptides are useful in providing immunological probes for
 differential identification of the tissue(s) or cell type(s). For a number of disorders of
 the above tissues or cells, particularly of the immune system, expression of this gene

at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
5 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 286 as residues: Lys-9 to Arg-14, or Met-38 to Asp-51.

The tissue distribution in immune tissues, particularly macrophages, combined
10 with the homology to a conserved human opsonin protein indicates that the protein product of this gene is useful for diagnosis and treatment of immune disorders, as well as the treatment and/or diagnosis of infectious disease. Moreover, the gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of
15 cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne,
20 neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's
25 disease; scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 5 formula of a-b, where a is any integer between 1 to 2418 of SEQ ID NO:48, b is an integer of 15 to 2432, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

10 FEATURES OF PROTEIN ENCODED BY GENE NO: 39

The translation product of this gene shares sequence homology with alpha-2 type I collagen which is thought to be important in tissue repair. (See, e.g., Genbank Accession No. 211607.)

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
 PQLPSCGRPWPGTASVFQSHTQGPREDPDP CRAQGSAGTHCPISLSPPRQ (SEQ ID NO:586),
 KTHPRALWSAGPSCALCPGGSGXTSP PQGAPRGIXWDRCPQIQVLEGQRVRF
 20 PSQPQHPSHLAPRGGCGWRPDSRPLLPTPSGLSSFFPLDA QCWPWRTVSWR
 (SEQ ID NO:587),
 AGAPGQQARLQYLLSFQGE GAPHEXGATGEGGDGAWEACXCXRCLLNWQA
 GGWGLQLSLMWLHRGPLRPPGVRWTPWAFLEACSWGPALSLLGSGHSLPGT
 HEQAAWSRGCGQH GQSPTQKCKSSKEPLAQAPPWDSPAAPPHQGFADVLER
 25 PTLEPFGVLAPPVPSALVEAAXQVLLREPQGGFXGTAAHRSRCWKGGSG (SEQ ID NO:588),
 MQLLFLLPHPSQLHASLPHSAALPCPRGESLTTASPAGAAGR XDAVPRCRH
 QAGRGWVPRGPCERGGGDRGKPRAVAWDXGSLRWAVWSARAGQGRSSEP
 APLASRRGYSTCCLSRGKGLPMRXGRRGRGVMVPGKPACAXGAC (SEQ ID
 30 NO:589), QHPSHLAPRGGCGWRPDSRPLLPTPSGLSSFFPL (SEQ ID NO:590),
 GVRWTPWAFLEACSWGPALSLLGSGHSLPG (SEQ ID NO:591),
 WDSAPAAPPHQGFADVLERPTLEPFGVLA (SEQ ID NO:592), and/or

RSSEPAPLASRRGYSTCCLSRGKGL PMR (SEQ ID NO:593). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the brain, and to a lesser extent, in the kidney and thymus

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain, kidney, endocrine, hematopoietic, and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, kidney, and immune disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, urogenital, renal, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and thymus, combined with the homology to an alpha-2 type I collagen protein indicates that the protein product of this gene is useful for the diagnosis and treatment of tissue repair, and brain, kidney, immune disorders. Moreover, this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal

chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1728 of SEQ ID NO:49, b is an integer of 15 to 1742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

The translation product of this gene shares sequence homology with mini-collagen which is thought to be important in tissue repair and tumor metastasis, and potentially in cellular migration, attachment, and/or chemotaxis. (See Genbank Accession No. gnl|PID|d1006976.)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
PGFRGPSGLGCSFFPRSLGRVLP GCQRPGAHADSSPPPTP (SEQ ID NO:594).
Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

5 This gene is expressed in ovarian cancer, and to a lesser extent, in dendritic cells and smooth muscle.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumor metastasis, tissue repair, integumentary, reproductive, and/or immune disorders, particularly cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor metastasis and tissue repair, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary, immune, hematopoietic, reproductive, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 288 as residues: Asn-2 to His-11.

The tissue distribution in dendritic cells, combined with the homology to the mini-collagen gene indicates that the protein product of this gene is useful for diagnosis and treatment of tumor metastasis and tissue repair. Alternatively, this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1473 of SEQ ID NO:50, b is an integer of 15 to 1487, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

This gene shares sequence homology with the HIV TAT protein. (See Genbank Accession No. 328416.)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

EDLKKPDPASLRAASC GEGKKRKACKNCTCGLAE ELEKEKSREQMSSQPKSA
 CGNCYLGDAFR CASC PYLGMPAFKPG EKVLLS (SEQ ID NO:595);
 EDLKKPDPASLRAASC GEGKKRKACKNCTCGLAE ELEKEKSREQMSSQPKSA
 CGNCYLGDAFR CASC PYLGMPAFKPG EKVLLSDSNLHD (SEQ ID NO:596);
 CGNCYLGDAFR CASC PYLGMPAFKPG EKVLLSDS (SEQ ID NO:597);
 SCGEGKKRKACKNCTCGLAE ELEKE (SEQ ID NO:598),
 SQPKSACGNCYLGDAFR CASC (SEQ ID NO:599); CCCVSKDQGIMGPGFR
 (SEQ ID NO:601),
 HSVTELQTPALSLISAMLPPSCLSELLVYSILCDTSQVAHNLLRAPEDSLTGCC
 DDIQCPSAPFHPQPHLTVALHLCPVVIYVNLQVLNLLHILTYLEILHVL (SEQ
 ID NO:602), LLVYSILCDTSQVAHNLLRAPEDS (SEQ ID NO:603),
 LTVALHLCPVVIYVNLQVLNLLHILT (SEQ ID NO:604), and/or
 REAGQNSERQYVSLSRDP (SEQ ID NO:600). Moreover, fragments and variants
 of these polypeptides (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the infant brain, and to a lesser extent, in the breast and testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, developmental, reproductive, brain, testes and breast disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, testes and breast disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, reproductive, testicular, breast, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 289 as residues: Pro-7 to Val-15.

The tissue distribution in infant brain tissue indicates that the protein product of this gene is useful for diagnosis and treatment of neural and other related disorders. Similarly the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia,

obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular or reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1314 of SEQ ID NO:51, b is an integer of 15 to 1328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

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In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

FFNALYVFRKPQAIFDSEKENKRKNPTKYNNPLRYIYFKVKLIFQFIPLANYKI
K (SEQ ID NO:605). Moreover, fragments and variants of this polypeptide (such as,

30 for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the

polynucleotide encoding this polypeptide are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

- 5 The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

 This gene is expressed primarily in the infant brain, human cerebellum, and to a lesser extent, in medulloblastoma.

- 10 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain related disorders, such as neurodegenerative conditions, medulloblastoma, and other cancers or proliferative conditions. Similarly, polypeptides and antibodies
15 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain related disorders and brain cancers, including medulloblastoma, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural,
20 developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 25 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 290 as residues: Thr-41 to Glu-47.

- The tissue distribution in infant brain and medulloblastoma indicates that the protein product of this gene is useful for diagnosis and treatment of human brain related disorders, brain cancers, and medulloblastoma. Similarly, the protein product
30 of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis,

encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1842 of SEQ ID NO:52, b is an integer of 15 to 1856, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 43

The translation product of this gene shares sequence homology with a phosphotyrosine-independent ligand for the lck SH2 domain which is thought to be important in signal transduction related to phosphotyrosine-independent ligand for the lck SH2 domain, which may implicate this protein as playing an essential role in

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regulating key cellular processes such as cellular division, and potentially in male fertility. (See Genbank Accession No. gi|1184951.)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 5 ESSGQARTLADPGPGWPRQQGMCFGSLTGLSTTPHGFLTVSAEADPRLIESLS
QMLSMGFSDEGGWLTRLQTKNYDIGAALDTIQYSKH (SEQ ID NO:606),
YSMVYTYHIFFIHSLLDGQLGWFHIFAIVSCAAPDIIFNSFAFSTYISKSCSFYLQ
NVSCIHSSLSIFNLFQCPIISCMEECNNWLTGLFLHFKIKRCR (SEQ ID
NO:607),
- 10 LSPSPRCCPWASLMKAAGSPGSCRPTMTSERLWTPSSIQSIPRRCDHFCPPLL
RAPLLSHSCVKLA (SEQ ID NO:608),
GWPRQQGMCFGSLTGLSTTPHGFLTVSAEADPRL (SEQ ID NO:609),
LGWFHIFAIVSCAAPDIIFNSFAFSTYISKSCS (SEQ ID NO:610),
SLSIFNLFQCPIISCMEECNNWLTG (SEQ ID NO:611), and/or
- 15 LMKAAGSPGSCRPTMTSERLWTPSSIQSI (SEQ ID NO:612). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
20 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

It is likely that this gene is a new member of a family of phosphotyrosine-independent ligands for the lck SH2 domains.

- 25 This gene is expressed primarily in the placenta, and to a lesser extent, in
endothelial cells and neutrophils.

- Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
30 reproductive, cardiovascular, immune, and infectious diseases. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the cardiovascular, reproductive, and immune system, and infectious diseases, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, cardiovascular, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 291 as residues: Ile-93 to Arg-98.

The tissue distribution in placenta and endothelial tissues, combined with the homology to a phosphotyrosine-independent ligand for the lck SH2 domain indicates that the protein product of this gene is useful for diagnosis and treatment of cardiovascular, reproductive, and immune system diseases, as well as infectious diseases. Moreover, the polypeptide of this gene may be able to modulate T or B cell development and/or T or B cell activation (e.g. by modulation of Lck activity). It may also be capable of modulating degradation of cellular proteins (e.g. cell cycle regulatory proteins stimulating expression of cell cycle dependent kinase inhibitors and arresting cell cycle progression at specific boundaries to thereby modulate cell proliferation). p62 acts to boost B cell response and may be used to treat disorders where this is beneficial, e.g. infections by pathogenic microorganisms, e.g. bacteria, viruses and protozoans. p62 can be used to expand T cell populations for treating infectious diseases or cancer, e.g. the resulting cells may be transduced to render them resistant to HIV infection. Inhibitors of p62 can be used to reduce B or T cell responses and may be used to treat a variety of autoimmune diseases, e.g. diabetes mellitus, arthritis, multiple sclerosis allergic reactions, Crohn's diseases etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 5 formula of a-b, where a is any integer between 1 to 1544 of SEQ ID NO:53, b is an integer of 15 to 1558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 44

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequences:

15 SSSSPRRPRELLGSLKTPLVRPHSAPLDLPGSFCXHTADPMGALHTRFWGRQT
 WIHRKLRLHGTSRLASKXGIQFLRNPSKTHTPRDAAFRDPGQTPDPQSLQAPS
 PSKCSAPNRATSVWSLKPRLLYKHRPSSDKTPPPGRQAPLLFFSAG (SEQ ID
 NO:613), and/or FLRNPSKTHTPRDAAFRDPGQTPDPQSLQA (SEQ ID NO:614).

Moreover, fragments and variants of these polypeptides (such as, for example,
 20 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.
 25 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the fetal brain, cerebellum, and to a lesser extent, in the placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
 30 and for diagnosis of diseases and conditions which include, but are not limited to,
 neural, developmental, or reproductive disorders, particularly cancers. Similarly,
 polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal cell related disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, reproductive, 5 vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 292 as residues: Thr-20 to Gly-28.

The tissue distribution in fetal brain, combined with the homology to proline-rich protein genes indicates that the protein product of this gene is useful for diagnosis and treatment of neuronal cell related disorders. Similarly, the protein product of this 15 gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, 20 hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in 25 synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Moreover, expression within fetal tissue and other cellular sources marked 30 by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions

involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:54, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

The translation product of this gene shares sequence homology with precerebellin of human, which is thought to be important in synaptic physiology. (See Genbank Accession No. gi|180251.) The cerebellum contains a hexadecapeptide, termed cerebellin, that is conserved in sequence from human to chicken. Three independent, overlapping cDNA genes have been isolated from a human cerebellum cDNA library that encode the cerebellin sequence. The longest gene codes for a protein of 193 amino acids that we term precerebellin. This protein has a significant similarity (31.3% identity, 52.2% similarity) to the globular (non-collagen-like) region of the B chain of human complement component C1q. The region of relatedness extends over approximately 145 amino acids located in the carboxyl terminus of both proteins. Unlike C1q B chain, no collagen-like motifs are present in the amino-terminal regions of precerebellin. The amino terminus of precerebellin contains three possible N-linked glycosylation sites. Although

hydrophobic amino acids are clustered at the amino terminus, they do not conform to the classical signal-peptide motif, and no other obvious membrane-spanning domains are predicted from the cDNA sequence. The cDNA predicts that the cerebellin peptide is flanked by Val-Arg and Glu-Pro residues. Therefore, cerebellin is not
5 liberated from precerebellin by the classical dibasic amino acid proteolytic-cleavage mechanism seen in many neuropeptide precursors. In Northern (RNA) blots, precerebellin transcripts, with four distinct sizes (1.8, 2.3, 2.7, and 3.0 kilobases), are abundant in cerebellum. These transcripts are present at either very low or undetectable levels in other brain areas and extraneural structures. A similar pattern
10 of cerebellin precursor transcripts are seen in rat, mouse, and human cerebellum. Furthermore, a partial genomic fragment from mouse shows the same bands in Northern blots as the human cDNA gene. During rat development, precerebellin transcripts mirror the level of cerebellin peptide. Low levels of precerebellin mRNA are seen at birth. Levels increase modestly from postpartum day 1 to 8, then increase
15 more dramatically between day 5 and 15, and eventually reach peak values between day 21 and 56. It has been observed that cerebellin-like immunoreactivity is associated with Purkinje cell postsynaptic structures. Thus, it is likely that this gene also have synaptic activity. Northern analysis showed a brain-specific 2.4kb message. This is consistent with the current insert size we have, suggesting our gene is full-
20 length and is brain-specific.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
QEGSEPVLLGECLVVCEPGRAAAGGPGGAALGEAPPGRVAFXAVRSHHHEP
AGETGNGTSGAIYFDQVLVNEGGGFDRASGSFVAPVRGVYSFRFHVVKVYN
25 RQTVQVSLMLNTWPVISAFANDPDVTREAAATSSVLLPLDPGDRVSLRLRRGX
STGW (SEQ ID NO:615), GETGNGTSGAIYFDQVLVNEGGGFDRASGSFVAPV
(SEQ ID NO:616), NDPDVTREAAATSSVLLPLDPGDRVS (SEQ ID NO:617),
FHVVKVYNRQT (SEQ ID NO:618), IYFDQVLVN (SEQ ID NO:619),
ESRERSGNRRGAEDRGTCGLQSPSA (SEQ ID NO:620),
30 EMPQFYFFLKLGLCLAQVPMQRGGIGARGSXPAVXGAREGRRKLSGAGF
LCLKDLGPSEDEEEARET (SEQ ID NO:621),
MPQFYFFLKLGLCLAQVPMQRGGIGARG (SEQ ID NO:622),

QATCSASGSPGQFGGCTPSPHGTGSCRHPGQGLRRSQRPGQSHRPRSPGPGRS
 RWPHWCHCRFPLLAHGGGFGPQQMPLAQGVPLPGLLPRAPLQQLGQAHPP
 GTPPPAGRALTPPGPTRPPGPEAPEPRAARDCVGD LVASVAWLPTWLRGSAT
 HKCPGLLPFCFRSSPWILTAGTLIVCPL (SEQ ID NO:623),

- 5 GCTPSPHGTGSCRHPGQGLRRSQRP (SEQ ID NO:624),
 SRWPHWCHCRFPLLAHGGGFGPQQMP (SEQ ID NO:625),
 DCVGD LVASVAWLPTWLRGSATHKCPGL (SEQ ID NO:626),
 DDRPRVQHQAHLD SLAVVHLHHMEPEAVDTPDRGYEGARGPVKATALVHQ
 DLVEVDGPTGAIAGFPCWLMVVASDRXKCHSPRGCLSQCSPGPPCSSSARL
 10 TDHQALPLQDGL (SEQ ID NO:627),
 YEGARGPVKATALVHQDLVEVDGPTGAIAGF (SEQ ID NO:628),
 MAPLVPLPVSPAGSWWWLRTAXNATRPGGASPRAAPPGPPAAARPGSQTTR
 HSPSSRTGSDPSWAHPAPRARSTRTKGSPGLCRGPGSQCG LAPNMAEGLCNP
 QVPRSSAPLLFLLSLDSHRRHPDSLPSLGS LNPLSIPVSQLCPASHSYSCCHCS
 15 S (SEQ ID NO:629), SSRTGSDPSWAHPAPRARSTRTKGSPGLC (SEQ ID
 NO:630), and/or RRHPDSLPSLGS LNPLSIPVSQLCPAS (SEQ ID NO:631).

Moreover, fragments and variants of these polypeptides (such as, for example,
 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
 20 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

- 25 This gene is expressed primarily in cerebellum and infant brain. By Northern
 analysis, a single transcript of 2.4 kb was observed in brain tissues.

- Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 neural and developmental disorders, particularly neuronal cell signal transduction,
 30 synaptic physiology, or proliferative conditions such as cancer. Similarly,
 polypeptides and antibodies directed to these polypeptides are useful in providing
 immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the neuronal cell signal transduction and synaptic physiology expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in cerebellum and infant brain, combined with the homology to the conserved precerebellin gene or gene family indicates that the protein product of this gene is useful for diagnosis and treatment of neuronal cell related disorders. Furthermore, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:55, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

10

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

STHASGPAPERLCLPERGTAPWGRRANDAA (SEQ ID NO:632),
 VRRWWLRTMGAAAHCTPEQRRPRRPATILGMDTQNILHTRLISLCSLSWVSL
 15 ASSFXXLAXRRKAIVVQKQSKISKKKKVEKXXLND SVNENSDTVGQIVHYI
 MKNEANADV LKAMVADNSLYDPESPVTPSTPGSPVSPGLCHQGGRQGSTS
 VAICIRWAVXSRGMCVIGVGTSGGT L (SEQ ID NO:633), and/or
 IMKNEANADV LKAMVADNSLYDPESPVTP (SEQ ID NO:634). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 20 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 25 these polypeptides are also encompassed by the invention.

This gene is expressed in fetal liver and spleen, and to a lesser extent in bone marrow, umbilical vein, and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
 30 and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune system, particularly hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoiesis and immune disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 294 as residues: Asp-30 to Glu-57.

The tissue distribution in fetal liver/spleen and bone marrow indicates that the protein product of this gene is useful for diagnosis and treatment of hematopoietic and immune disorders. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1589 of SEQ ID NO:56, b is an integer of 15 to 1603, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares sequence homology with a 12 kD nucleic acid binding protein of Feline calicivirus which is thought to be important in viral replication and may implicate this protein as playing an integral role in the development of host-viral inhibitors and/or novel vaccines. (See Genbank Accession No. 59264).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

HCHLWASGSCCLACFFPGGLTRDAAQQHVTKSYSPPYLSQTSLSCLVFQPVWLW
PEYTFWNLFMAILQFQMNHSVLQXXGPRHVCRGAEAAAAGEGPGYSDRAAA
ARGAPSQWGRPAPKDTLAQTLGQTGRASPRLPAGLGTQAS (SEQ ID NO:635),
PAPKDTLAQTLGQTGRASPRLPAGLGTQ (SEQ ID NO:636),
TIACFSXKARDMYAEERKRQQLERDQATVTEQLLREGLQASGDAQLRRLRL
HKLSARREERVQGFLQALELKRADWLARLGTASA (SEQ ID NO:637), and/or
LRLRLHKLSARREERVQGFLQALELKR (SEQ ID NO:638). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention..

This gene is expressed primarily in human cardiomyopathy tissue, and to a lesser extent, in T helper cells, fetal brain and synovial sarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular, immune, or developmental disorders, particularly cardiomyopathy which occur secondary to viral infections. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, neural, developmental, skeletal, immune cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 295 as residues: Trp-20 to Cys-26.

The tissue distribution in cardiomyopathy tissue, combined with the homology to a viral 12 kD nucleic acid binding protein indicates that the protein product of this gene is useful for diagnosis and intervention of cardiomyopathy, including those caused by ischemic, hypertensive, congenital, valvular, or pericardial abnormalities. The gene expression pattern may be the consequence or the cause for these conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:57, b is an

integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 48

The translation product of this gene shares sequence homology with tumor necrosis factor related gene product, which is thought to be important in tumor necrosis, bacterial and viral infection, immune diseases and immunoreactions.

10 In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:
 KMNSIPWQIPKITPXLNANLVIVECKPLWFCIGTIKQLKLWNQVFMGFKSMFF
 RIGKLNLYLFTIPYCYLFIDNILGIFYLSILGAQGIKYNFYIQRIFTCLLNLNKIHNSN
 LA (SEQ ID NO:639), LWFCIGTIKQLKLWNQVFMGFKSMFFR (SEQ ID
 15 NO:640), YSILGAQGIKYNFYIQRIFTCLLNLN (SEQ ID NO:641), and/or
 TFKLVRFLE (SEQ ID NO:642). Moreover, fragments and variants of these
 polypeptides (such as, for example, fragments as described herein, polypeptides at
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent
 20 conditions, to the polynucleotide encoding these polypeptides) are encompassed by
 the invention. Antibodies that bind polypeptides of the invention are also
 encompassed by the invention. Polynucleotides encoding these polypeptides are also
 encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
 25 10. Accordingly, polynucleotides related to this invention are useful as a marker in
 linkage analysis for chromosome 10.

This gene is expressed primarily in colon, and to a lesser extent, in ovarian
 and breast cancers.

Polynucleotides and polypeptides of the invention are useful as reagents for
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 gastrointestinal, reproductive, colon, ovarian, breast disorders, particularly cancers.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the colon, ovary and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, reproductive, colon, ovarian, breast, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in colon tissue, combined with the homology to tumor necrosis factors indicates that the protein product of this gene is useful for the intervention of cancers of the colon, ovary and breast, particularly because TNF family members are known to be involved in the tumor development. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:58, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

The translation product of this gene shares sequence homology with mucins, such as epithelial mucin, which are thought to be important in extracellular matrix

functions such as protection, lubrication and cell adhesion, which are important in a variety of functions, particularly immune chemotaxis and infiltration (See for example Genbank Accession No. R68002).

- In specific embodiments, polypeptides of the invention comprise, or
 5 alternatively consists of, an amino acid sequence selected from the group:
 PRSRPALRPGRQRPPSHSATSGVLRPRKKPDP (SEQ ID NO:643),
 RKSFAPVLTWNAIQAGRGRVLCYTRPPPASSSFSALVPDGNRMEGLRITYFL
 NAFDPGTDYLYLFPSFTVTFQHCLTVRWAFESLQVPQNRPERWASHPLPTH
 XPAYLPDNQVXMSASG (SEQ ID NO:644),
 10 GNRMEGLRITYFLNAFDPGTDYLYLF (SEQ ID NO:645), and/or
 FQHCLTVRWAFESLQVPQNRPERWASHPLP (SEQ ID NO:646). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 15 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

- Moreover, this gene maps to chromosome 22q11.2-qter, and therefore, can be
 20 used as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in corpus colosum.

- Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 25 tumors, especially of the corpus colosum, as well as metastatic lesions, autoimmune
 conditions, and integumentary disorders. Similarly, polypeptides and antibodies
 directed to these polypeptides are useful in providing immunological probes for
 differential identification of the tissue(s) or cell type(s). For a number of disorders of
 the above tissues or cells, particularly of the corpus colosum and other solid tissues,
 30 expression of this gene at significantly higher or lower levels may be routinely
 detected in certain tissues or cell types (e.g., integumentary, autoimmune, neural, and
 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5 The tissue distribution in corpus colosum, combined with the homology to mucins indicates that the protein product of this gene is useful for serum tumor markers or immunotherapy targets because tumor cells have greatly elevated levels of mucin expression and shed the molecules into the epithelial tissues. Moreover, the protein product of this gene is useful for the treatment, diagnosis, and/or prevention of
- 10 various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder,
- 15 psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox,
- 20 molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, Athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as
- 25 dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.
- 30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 1201 of SEQ ID NO:59, b is an integer of 15 to 1215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

10 FEATURES OF PROTEIN ENCODED BY GENE NO: 50

This gene is expressed primarily in CD34 depleted buffy coat cord blood and primary dendritic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
15 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders and immunological disorders, particularly those related to developmental or reproductive conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for
20 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid,
25 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34 depleted buffy coat cord blood and primary
30 dendritic cells indicates that the protein product of this gene is useful for the diagnosis and treatment of hematopoietic and immune disorders. Secreted or cell surface proteins in the above tissue distribution often are involved in cell activation (e.g.

cytokines) or molecules involved in cell surface activation. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages.

5 The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells
10 and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:60, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

The translation product of this gene shares sequence homology with Interferon induced 1-8 gene encoded polypeptide, which is thought to be important in binding to
30 retroviral rev responsive elements and may be beneficial in the development of novel inhibitors of host-viral interactions leading to effective viral vaccines.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MTLITPSXKLTFXKGNKSWSSRACSSSTLVDP (SEQ ID NO:647),

FLFLHAVDPWPSNG (SEQ ID NO:648),

5 WSCQSGVFLVFTGCSVLCQMLSGAVVWRRSAPEDSAVWQASINKPRGKGR
HGIKGENTSV (SEQ ID NO:649), and/or LVFTGC

SVLCQMLSGAVVWRRSAPEDSAVWQASI (SEQ ID NO:650). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in CD34 positive cells and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
viral infection, such as AIDS, and other immune or hematopoietic disorders.

20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in
providing immunological probes for differential identification of the tissue(s) or cell
type(s). For a number of disorders of the above tissues or cells, particularly of the
immune system, expression of this gene at significantly higher or lower levels may be
routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and
25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum,
plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
from an individual having such a disorder, relative to the standard gene expression
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 299 as residues: Gln-51 to Trp-62.

The tissue distribution in neutrophils and CD34 positive cells, combined with the homology to interferon induced gene 1-8 indicates that the protein product of this gene is useful for the intervention of retroviral infection including HIV. The factor may be involved in viral stability or viral entry into the cells. Alternatively, the virus/factor complex may elicit the cellular immune reaction and could possibly play a beneficial role in the development of effective inhibitors of host-viral interactions, such as exists for novel viral vaccines. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 604 of SEQ ID NO:61, b is an

integer of 15 to 618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 52

This gene shares sequence homology to immunoglobulin lambda chain (See Genbank Accession No. 2865484). Therefore it is likely that this gene has activity similar to an immunoglobulin lambda chain and may play a beneficial role in the
10 development of effective immunotherapy-based toxins.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
GHPSPALSIAPSDGSQPCDEVPIYGEAHVTRYCKKPLTNSHLETEAQSSSL
(SEQ ID NO:651),
15 NNKHYLSFCGSGFCPVYLGFTGLASHQAVKVLVAVIIPRQDRERICLQAQV
GRIHLRGCWTGPPFLDGYWSEAFYNTLSRGPLHRAPHHMATGFHQREQWKE
QEKGDQGRHRSLLVASPQKRCYFCCILXVRSESLGPGVEFYXGVNGRR (SEQ
ID NO:652), ERICLQAQVGRIHLRGCWTGPPFLDGYWSEAF (SEQ ID NO:653),
SDGSQPCDEVPIYGEAHVTRYCKKPL (SEQ ID NO:654), and/or
20 HQREQWKEQEKGDQGRHRSLLVASPQK (SEQ ID NO:655). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
25 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in Hodgkin's lymphoma.

Polynucleotides and polypeptides of the invention are useful as reagents for
30 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
Hodgkin's lymphoma and other immune or hematopoietic disorders. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be
5 routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the
10 disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 300 as residues: Pro-27 to Thr-32.

The tissue distribution in Hodgkin's lymphoma, combined with the sequence homology to immunoglobulin lambda chain protein indicates that the protein product
15 of this gene is useful for the diagnosis of Hodgkin's lymphoma, since the elevated expression and secretion by the tumor mass may be indicative of tumors of this type. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an
20 agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:62, b is an

integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 53

This gene has extensive homology to cDNA for Homo sapiens mRNA for the ISLR gene(See Genbank Accession No. AB003184). This protein is considered to be a new member of the Ig superfamily and contains a leucine-rich repeat (LRR) with
10 conserved flanking sequences and a C2-type immunoglobulin (Ig)-like domain. These domains are important for protein-protein interaction or cell adhesion, and therefore it is possible that the novel protein ISLR may also interact with other proteins or cells. The ISLR gene was mapped on human chromosome 15q23-q24 by fluorescence in situ hybridization (See Medline Article No. 97468140). Homology
15 to the ISLR gene has been confirmed by another independent group as well (See Genbank Accession No. Hs.102171).

This gene is expressed in a number of tissues including human retina, heart, skeletal muscle, prostate, ovary, small intestine, thyroid, adrenal cortex, testis, stomach, spinal cord, fetal lung and fetal kidney tissues, colon, tonsil and stomach
20 cancer, and to a lesser extent in endometrial stromal cells treated with estradiol, breast tissue, synovium, lymphoma, and number of other tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
25 tumors of colon, ovary, breast, and integumentary or immune origins. However, due to the wide range of expression in various tissues, protein may play a vital role in the development of cancer in other tissues as well, not just those mentioned above. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell
30 type(s). For a number of disorders of the above tissues or cells, particularly of the colon, ovary and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune,

integumentary, reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, breast milk, seminal fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Additionally, this gene maps to chromosome 15q23-q24, and therefore, can be used as a marker in linkage analysis for chromosome 15.

The tissue distribution in tumors of colon, ovary, and breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds); stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction, etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:63, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

The gene has homology to a multidrug resistance gene 1 (See Genbank Accession No. P06795).

Preferred polynucleotide fragments comprise the following sequence:

15 gcttcgtgtccaacctcttgcccttcgcctgtgtgcctggagccagtcaccacgctcgcgtttcctctgtagtgtcacac
gggtcccagcaccgatggcattccctttgccctgagctgcagcgggtcccttttgcctccttcccctcaggtagcctctctc
ccccggggccactcccgggggtgaggggggtacccctcccagtgttttattcctgtggggctcaccccaaagtattaaaa
gtagctttgtaa (SEQ ID NO:656),

gcttcgtgtccaacctcttgccttcgcctgtgtgcctggagccagtcaccacgctcgcgttctcctgtagtgtcacac
gggtccagcaccgatggcattcccttgcctgagctgcagcgggtccctttgtgttccctccctcaggtagcctctctc
20 cccctgggccactcccgggggtgagggggtacccttccagtgttttattcctgtggggctaccccaaagtattaaaa
gtagctttgtaa (SEQ ID NO:657),

gcttcgtgtccaacctcttgcccttcgcctgtgtgcctggagccagtcccaccacgctcgcgtttcctcctgtagtgtcacaca
gggtccagcaccgatggcattcccttggcctgagctcgcagcggtgcccttttgtcttcctccccctcaggtagcctctctc
ccccctgggccactccccgggggtgaggggttacccctcccagtgtttttatctctgtggggctaccccaaagtattaaaa
25 gtagctttgtaa (SEQ ID NO:658). Also preferred are polypeptides comprising one or
more of the fragments encoded by these polynucleotide fragments.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

FRINRLTIGXAVAMTRGNQRELARQKNMKKQSDSVKGKRRDDGLSAAARK
30 QRDSEI (SEQ ID NO:659), AVAMTRGNQRELARQKNMKKQSDSVKGKR (SEQ
ID NO:660),
KSRATRLRESAEMTGFLPPASRGTRRSCSRSRKROTRRRRNPSSFVASCPTLL

PFACVPGASPTTLAFPPVVLTPSTDGIPFALSLQRVPFVLPSPQVASLPLGHSR
G (SEQ ID NO:661), LRESAEMTGFLPPASRGTRRSCSRS (SEQ ID NO:662),
and/or VVLTPSTDGIPFALSLQRVPFVLPSPQVA (SEQ ID NO:663). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
5 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
10 these polypeptides are also encompassed by the invention.

This gene is expressed primarily in lung, esophagus, leukemia (Jurkat cells),
breast cancers and to a lesser extent, in macrophages treated with GM-CSF fetal
tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for
15 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
immune, developmental, or pulmonary disorders, particularly cancers. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
immunological probes for differential identification of the tissue(s) or cell type(s).
20 For a number of disorders of the above tissues or cells, particularly of the solid
tumors, lung and leukemia, expression of this gene at significantly higher or lower
levels may be routinely detected in certain tissues or cell types (e.g., immune,
developmental, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g.,
lymph, pulmonary surfactant and sputum, amniotic fluid, serum, plasma, urine,
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
the expression level in healthy tissue or bodily fluid from an individual not having the
disorder. Furthermore, due to the high expression level in lung tissue and the
proposed function of the multidrug resistance protein 1 gene as the efflux pump
30 responsible for low-drug accumulation in multidrug-resistant cells, protein as well
mutants thereof, may also be beneficial as a target for gene therapy, particularly for
the chronic patient.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 302 as residues: Met-1 to Lys-16.

The tissue distribution cancers and fetal tissues indicates that the protein product of this gene is useful for the detection of cells in active proliferation, such as
5 cancers. The gene products may be used for cancer markers or immunotherapy target. Similarly, the secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are
10 cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for
15 treating wounds); stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction, etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for
20 regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 574 of SEQ ID NO:64, b is an

integer of 15 to 588, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 55

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

LLSTSHLLTQSYSFNKRSHSFAWKNAHCILQSENNELQNSVYTYVCIYVHF

10 ICTFLCDI (SEQ ID NO:664), and/or KRSHSFAWKNAHCILQSENNELQNSVYTYVCI (SEQ ID NO:665). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the
15 polynucleotide encoding these polypeptides) are encompassed by the invention, Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on the X
20 chromosome. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for the X chromosome.

This gene is expressed primarily in the brain, and to a lesser extent, in the developing embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for
25 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disease states and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).
30 For a number of disorders, including X-linked disorders, of the above tissues or cells, particularly of the neurological, developmental systems, and cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely

detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
5 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neural tissue indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's
10 Disease, Klinefelter's, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually- or X-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the
15 protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of
20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 931 of SEQ ID NO:65, b is an
25 integer of 15 to 945, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

30

The translation product of this gene shares sequence homology with paxillin, which is thought to be important in mediating signal transduction from growth factor

receptors to the cytoskeleton. Moreover, in normal hematopoietic cells and myeloid cell lines, tyrosine phosphorylation of paxillin has been shown to be rapidly and transiently induced by interleukin-3 and several other hematopoietic growth factors. The predicted structure of paxillin implicates this molecule in protein-protein
 5 interactions involved in signal transduction from growth factor receptors and the BCR/ABL oncogene fusion protein to the cytoskeleton.

Preferred polynucleotide fragments comprise the following sequence:

tggtcactgtcttacaatcactgctgtggaatcatgataccacttttagctcttgcattctccttcagtgtattttgttttcaaga
 ggaagtagattttaactggacaactttgagtactgacatcattgataaataaactggcttggtttcaa (SEQ ID

10 NO:666). Also preferred are polypeptide fragments encoded by these polynucleotide fragments.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

LDELMAHLTEMQAKVAVRADAGKKHLPDKQDHKASLD SMLGGLEQELQDL
 15 GIATVPKGHCASCQKPIAGKVIHALGQSWHPEHFVCTHCKEEIGSSPFFERSGL
 XYCPNDYHQLFSPRCAYCAAPILDKVLTAMNQ TWHPEHFFCSHCGEVFGAE
 GFHEKDKKPYCRKDFLAMFSPKCGGCNRPVLENYLSAMDTVWHPECFVCG
 DCFTSFSTGSFFELDGRPFCELHYHRRGTLCHGCGQPITGRCISAMGYKFHP
 EHFVCAFCLTQLSKGIFREQNDKTYCQPCFNKLF (SEQ ID NO:667),
 20 KASLD SMLGGLEQELQDLGIATVPKGHCASCQKPIAGKVIHAL (SEQ ID
 NO:668),

CPNDYHQLFSPRCAYCAAPILDKVLTAMNQ TWHPEHFFCSHCGEVFGAEG
 (SEQ ID NO:669),
 DKKPYCRKDFLAMFSPKCGGCNRPVLENYLSAMDTVWHPECFVCGDCFTSF
 25 STGSFFELDGRPFCEL (SEQ ID NO:670),
 CGQPITGRCISAMGYKFHPEHFVCAFCLTQLSKGIFREQNDKTYCQ (SEQ ID
 NO:671),

HKSLAGAXVYTTNIQELNVYSEAQEPKESPPPSKTSAAAQLDELMAHLTEMQ
 AKVAVRADAGKKHLPDKQDHKASLD SMLGGLEQELQDLGIATVPKGHCAS
 30 CQKPIAGKVIHALGQSWHPEHFVCTHCKEEIGSSPFFERSGLXYCPNDYHQLF
 SPCAYCAAPILDKVLTAMNQ TWHPEHFFCSHCGEVFGAEGFHEKDKKPYC
 RKDFLAMFSPKCGGCNRPVLENYLSAMDTVWHPECFVCGDCFTSFSTGSFFE

- LDGRPFCELHYHHRRGTLCHGCGQPITGRCISAMGYKFHPEHFVCAFCLTQLS
 KGIFREQNDKTYCQPCFNKLFPL (SEQ ID NO:672),
 NVYSEAQEPKESPPPSKTSAAA (SEQ ID NO:673),
 DSMLGGLEQELQDLGIATVPKGHCAS (SEQ ID NO:674),
 5 YLSAMDTVWHPECFVCGDCFTSFSTG (SEQ ID NO:675),
 RCISAMGYKFHPEHFVCAFCLTQLSK (SEQ ID NO:676),
 PTRPVLFSTCQSCSSRPVRQEHLGCRTEELDALLEELERSTLQDSDEYSNP
 APLPLDQHSRKETNLDETSELSIQDNTSPLPAXSCILPISRSSMSTVKPKSQRN
 HHHLLKRQQLLSWMSSWLT (SEQ ID NO:677),
 10 PVRQEHLGCRTEELDALLEELERSTLQ (SEQ ID NO:678),
 SCILPISRSSMSTVKPKSQRN (SEQ ID NO:679), WHPEHFVCTHC (SEQ ID
 NO:680), LFSPRC (SEQ ID NO:681), PILDKV (SEQ ID NO:682), TWHPEHFF
 (SEQ ID NO:683), EGFHEKD (SEQ ID NO:684), KFHPEHFVCAFCL (SEQ ID
 NO:685), PITGRCI (SEQ ID NO:686), and/or HPEHFVC (SEQ ID NO:687).
 15 Moreover, fragments and variants of these polypeptides (such as, for example,
 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 20 bind polypeptides of the invention are also encompassed by the invention.
 Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

- 25 This gene is expressed primarily in brain, and to a lesser extent in the developing embryo.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
 30 neurological disease states and developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain, combined with the homology to the conserved paxillin gene, indicates that the protein product of this gene is useful for the treatment and or detection of disease states associated with abnormal signal transduction in brain and/or the developing embryo. This would include treatment or detection of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder and also in the treatment and or detection of embryonic development defects. Moreover, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1852 of SEQ ID NO:66, b is an

integer of 15 to 1866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

5 **FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

RIYCS EDTFSPXAESGVSWQSSVSQLYQDYE (SEQ ID NO:688). Moreover,
10 fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of
15 the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in fetal spleen, brain, and to a lesser extent, in six week old embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, neurological disorders, and developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell
25 type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or
30 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 305 as residues: Arg-28 to Gly-34.

The tissue distribution in fetal spleen indicates that the protein product of this gene is useful for the treatment/detection of immune disorders such as arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. In addition the expression of this gene in the early embryo, indicates a key role in embryo development, and hence the gene or gene product could be used in the treatment and or detection of embryonic developmental defects. This would include treatment or detection of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder and also in the treatment and or detection of embryonic development defects. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1138 of SEQ ID NO:67, b is an integer of 15 to 1152, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

The translation product of this gene shares sequence homology with the gene disrupted in the neurodegenerative disease dentatorubal-pallidoluyisian atrophy. Moreover, the translation product of this gene also shares homology with the

GRASP65 protein, a protein involved in the stacking of Golgi cisternae (See Genbank Accession No. AF015264).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 5 MGSSQSVEIPGGGTEGYHVLRVQENSPGHRAGLEPFFDFIVSINGSRLNKDND
TLKDLLKXNVEKPKV KMLIYSSKTLELRETSVTPSNLWGGQGLLGVSIRFCSFD
GANENVWHVLEVESNSPAALAGLRPHSDYIIGADTMNESEDLFSLIETHEAK
PLKLYVYNTD TDNCREVIITPNSAWGGEGSLGCGIGYGYLHRIPTRPFEEGKKI
SLPGQMAGTPITPLKDGFTVEVQLSSVNPPSLSPPGTTGIEQSLTGLSISSTPPAVS
- 10 SVLSTGVPTVPLLPPQVNQSLTSVPPMNPATTLPGLMPLPAGLPNLPNLPNLNL
PAPHIMPGVGLPELVNPGLPPLPSMPPRNLPGLAPLPSEFLPSFPLVPESSSAA
SSGELLSSLPTSNA PSDPATTTAKADAASSLTVDVTPPTAKAPTTVEDRVGD
STPVSEKPVSAAVDANASESP (SEQ ID NO:689),
SVEIPGGGTEGYHVLRVQENSPGHRAGLEPFFDFIVSINGSRLNKDNDTLKDL
- 15 LKXNVEKPKV KMLIYSSKTLELRETSVTPSNLWGGQGLLGVSIRFCSFDGANEN
VWH (SEQ ID NO:690),
ESNSPAALAGLRPHSDYIIGADTMNESEDLFSLIETHEAKPLKLYVYNTD TD
NCREVIITPNSAWGGEGSLGCGIGYGYLHRIPTRPFEEGKKISLPGQMAGTPIT
PLKDGFTVEVQLSSVNPPSLSPPGTTGIEQSLTGLSISS (SEQ ID NO:691),
- 20 ESNPAALAGLRPHSDYIIGADTMNESEDLFSLIETHEAKPLKLYVYNTD TD
NCREVIITPNSAWGGEGSLGCGIGYGYLHRIPTRPFEEGKKISLPGQMAGTPIT
PLKDGFTVEVQLSSVNPPSLSPPGTTGIEQSLTGLSISS (SEQ ID NO:692)
RIPTRPFEEGKKISLPGQMAGTPITPLKDGFTVEVQLSSVNPPSLSPPGTTGIEQSL
TGLSISSTPPAVSSVLSTGVPTVPLLPPQVNQSLTSVPPMNPATTLPGLMPLPA
- 25 GLPNLPNLPNLPAPHIMPGVGLPELVNPGLPPLPSMPPRN (SEQ ID NO:693),
PGLPPLPSMPPRNLPGLAPLPSEFLPSFPLVPESSSAASSGELLSSLPTSNA PS
DPATTTAKADAASSLTVDVTPPTAKAPTTVEDRVGDSTPVSEKPVSAAVDAN
(SEQ ID NO:694), AWGGEGSLGCGIGYGYLHRIPT (SEQ ID NO:695),
SPAALAGLRP (SEQ ID NO:696), and/or WGGQGLLG (SEQ ID NO:697).
- 30 Moreover, fragments and variants of these polypeptides (such as, for example,
fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the

polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 The gene encoding the disclosed cDNA is believed to reside on chromosome

2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in prostate cancer, and to a lesser extent, in the pineal glands and in fetal lung.

10 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, endocrine, reproductive, pulmonary, developmental disorders.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in
15 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous, pulmonary, and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neurological, endocrine, reproductive, pulmonary, developmental, and cancerous and
20 wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, pulmonary surfactant and sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 306 as residues: Asn-9 to Leu-14.

The abundance of this gene in the pineal gland and its homology to a gene disrupted in the neurodegenerative disease state Dentatorubral-pallidoluysian atrophy indicates that this gene may be useful in the treatment and/or detection of other
30 neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Alternatively, the

abundance of this gene in fetal lung would suggest that misregulation of the expression of this protein product in the adult could lead to lymphoma or sarcoma formation, particularly in the lung; that it may also be involved in predisposition to certain pulmonary defects such as pulmonary edema and embolism, bronchitis and cystic fibrosis; and thus the gene or the gene product encoded by the gene could be used in the detection and/or treatment of these pulmonary disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2469 of SEQ ID NO:68, b is an integer of 15 to 2483, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

RNGALLDKNFFNANSHFPVKGERIRRR (SEQ ID NO:698). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in the developing embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing, proliferating, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene primarily in the embryo indicates the gene plays a key role in embryo development, and that the gene or the protein encoded by the gene could be used in the treatment and or detection of developmental defects in the embryo or in infants. Similarly, the relatively specific expression of this gene product during embryogenesis indicates that it may be a key player in the proliferation, maintenance, and/or differentiation of various cell types during development. It may also act as a morphogen to control cell and tissue type specification. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 522 of SEQ ID NO:69, b is an integer of 15 to 536, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

This gene displays homology to nestin, an intermediate filament protein, the expression of which correlates with the proliferation of central nervous system progenitor cells and is useful in the identification of brain tumors.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

RGSGFGWTSFPRPLPTELTCPGFHRERAFPPDGRVRGVRGWGIRRGCAVWG
 VGACGCSPGSSWRGSAHRASGPADLPVACRXEGGADSPSLLPSPP (SEQ ID
 NO:699), AVWGVGACGCSPGSSWRGSAHRA (SEQ ID NO:700), YRP
 TMEKMKQVVTQTRWMRPDAKRANRRHRRISGKIFAWNPLPKTRFSRLLKAV
 SENTKRPEPSRPPWMVSHSVEAS (SEQ ID NO:701), and/or
 FAWNPLPKTRFSRLLKAVSENTKRPEP (SEQ ID NO:702). Moreover, fragments
 and variants of these polypeptides (such as, for example, fragments as described
 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%
 identical to these polypeptides and polypeptides encoded by the polynucleotide which
 hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in kidney, and to a lesser extent, in brain.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal disorders and neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
10 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the excretory and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, urogenital, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,
15 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
20 NO: 308 as residues: Thr-130 to Asn-137.

The tissue distribution in brain and kidney, combined with the homology to the conserved nestin protein, indicates that the protein product of this gene is useful for the detection and/or treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease,
25 schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, its abundance in kidney indicates that it is useful in the treatment and detection of acute renal failure and other disease states associated with the kidney, such as nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome,
30 glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed

against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 560 of SEQ ID NO:70, b is an integer of 15 to 574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 61

This gene shares homology with the latrophilin-related protein 1 precursor as well as the calcium-independent alpha-latrotoxin receptor. alpha-Latrotoxin, a black widow spider neurotoxin, can bind to high affinity receptors on the presynaptic plasma membrane and stimulate massive neurotransmitter release in the absence of Ca^{2+} . Neurexins, previously isolated as alpha-latrotoxin receptors, require Ca^{2+} for their interaction with the toxin and, thus, may not participate in the Ca^{2+} -independent alpha-latrotoxin activity. However, latrophilin binds alpha-Latrotoxin with high affinity in the presence of various divalent cations (Ca^{2+} , Mg^{2+} , Ba^{2+} , and Sr^{2+}) as well as in EDTA. This presumably membrane-bound protein is localized to and differentially distributed among neuronal tissues, with about four times more latrophilin expressed in the cerebral cortex than in the cerebellum; subcellular fractionation showed that the protein is highly enriched in synaptosomal plasma membranes.

30 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
IYKVFRTAGLKPESCFENIRSCARXXXXXXXXXXXXXWIFGVLHVHASV

VTAYLFTVSNAFQGMFIFLFLCVLSRKIQEEYYRLFKNVPCC (SEQ ID NO:703),

WIFGVLHVHASVVTAYLFTVSNAFQGMFIFLFLCVLSRKIQEEYYRLFKNVPCC (SEQ ID NO:704), IYKVFRHTAGLKPEVSCFENIRSCAR (SEQ ID NO:705),

5 IYKVFRHTAGLKPEVSCFENIRSCARGALALLFLLGTTWIFGVLHVHASVVTAYLFTVSNAFQG (SEQ ID NO:706), and/or

EVSCFENIRSCARGALALLFLLGTTWIFGVLH (SEQ ID NO:707). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 The translation product of this gene also shares sequence homology with CD 97, a seven transmembrane bound receptor (see Genbank Accession No. 2213659). The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

20 This gene is expressed primarily in infant brain and in endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, vascular, and hematopoietic disorders. Similarly, polypeptides and

25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, neural,

30 hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 309 as residues: Lys-13 to Leu-21.

5 The tissue distribution in infant brain genes suggest that the protein product may be useful in the detection and/or treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder, while its expression in hematopoietic cell
10 types indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma and immunodeficiency diseases. Moreover, the expression within endothelial tissue indicates that the protein product of this gene may show utility in the treatment and/or prevention of a variety of vascular disorders, which include, but are not limited to microvascular disease,
15 atherosclerosis, stroke, embolism, and aneurysm. Furthermore, expression within infant tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also
20 be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
25 related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
30 formula of a-b, where a is any integer between 1 to 918 of SEQ ID NO:71, b is an integer of 15 to 932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

- 5 In a specific embodiment, polypeptides of the invention, comprise or alternatively consist of, one or more of the following amino acid sequences:
TTILRTCTIVCFYYWFNGVMVLLFFLDRNLLTFNQASIMPFSNTDFLHCLSFK
KKLMLLRYIFYVVL TGPTLSLKG DENQIKNLFT (SEQ ID NO:708);
IVCFYYWFNGVMVLLFFLDRNLL (SEQ ID NO:709), and/or
- 10 LLRYIFYVVL TGPTLSLKG DENQI (SEQ ID NO:710). Polynucleotides encoding these polypeptides are also encompassed by the invention as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
- 15 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.
- 20 Also preferred are polypeptides, comprising or alternatively consisting of, the mature polypeptide which is predicted to consist of residues:
PTCYSRMRALSQEITRDFNLLQVSEPSEPCVRYLPRLYLDIHNYCVLDKLRDF
VASPPCWKVAQVDSLKDKARKLYTIMNSFCRRDLVFLDDCNALEYPIPVTT
VLPDRQR (SEQ ID NO:1245) of the foregoing sequence (SEQ ID NO:310), and
- 25 biologically active fragments of the mature polypeptide (e.g., fragments that induce hematopoiesis). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
- 30 encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are

also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Figures 5A-5B show the nucleotide (SEQ ID NO:72) and deduced amino acid sequence (SEQ ID NO:310) corresponding to this gene.

5 Figure 6 shows an analysis of the amino acid sequence (SEQ ID NO:310). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the
10 highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 6 are also represented in tabular form in Table 5.
15 The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 6, and Table 5: "Res": amino acid residue of SEQ ID NO:310 and Figures 5A-5B; "Position": position of the corresponding residue within SEQ ID NO:310 and Figures 5A-5B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions -
20 Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible
25 Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet
30 forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-

forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figures 5A-5B and/or Table 5, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 5 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figures 5A-5B, but may, as shown in Table 5, be represented or identified by using tabular representations of the data presented in Figure 6. The DNA*STAR computer algorithm used to generate Figure 6 (set on the original default parameters) was used to present the data in Figure 6 in a tabular format (See Table 5). The tabular format of the data in Figure 6 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 72, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO:72. By a fragment at least 20 nt in length, for example, is intended fragments

which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:72. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

- 5 Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to
10 about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to about 900, from about 901 to about 950, or from about 951 to about 985 of SEQ ID NO:72, or the complementary strand thereto, or the cDNA
15 contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.
- Preferred polypeptide fragments of the invention comprise, or alternatively consist of,
20 the secreted protein having a continuous series of deleted residues from the amino or the carboxyl terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-136 where m is an integer from 2 to 136, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:310. More in particular, the invention provides polynucleotides encoding
25 polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: R-2 to R-136; T-3 to R-136; P-4 to R-136; G-5 to R-136; P-6 to R-136; L-7 to R-136; P-8 to R-136; V-9 to R-136; L-10 to R-136; L-11 to R-136; L-12 to R-136; L-13 to R-136; L-14 to R-136; A-15 to R-136; G-16 to R-136; A-17 to R-136; P-18 to R-136; A-19 to R-136; A-20 to R-136; R-21 to R-136; P-22 to R-136;
30 T-23 to R-136; P-24 to R-136; P-25 to R-136; T-26 to R-136; C-27 to R-136; Y-28 to R-136; S-29 to R-136; R-30 to R-136; M-31 to R-136; R-32 to R-136; A-33 to R-136; L-34 to R-136; S-35 to R-136; Q-36 to R-136; E-37 to R-136; I-38 to R-136; T-39 to

R-136; R-40 to R-136; D-41 to R-136; F-42 to R-136; N-43 to R-136; L-44 to R-136;
 L-45 to R-136; Q-46 to R-136; V-47 to R-136; S-48 to R-136; E-49 to R-136; P-50 to
 R-136; S-51 to R-136; E-52 to R-136; P-53 to R-136; C-54 to R-136; V-55 to R-136;
 R-56 to R-136; Y-57 to R-136; L-58 to R-136; P-59 to R-136; R-60 to R-136; L-61 to
 5 R-136; Y-62 to R-136; L-63 to R-136; D-64 to R-136; I-65 to R-136; H-66 to R-136;
 N-67 to R-136; Y-68 to R-136; C-69 to R-136; V-70 to R-136; L-71 to R-136; D-72
 to R-136; K-73 to R-136; L-74 to R-136; R-75 to R-136; D-76 to R-136; F-77 to R-
 136; V-78 to R-136; A-79 to R-136; S-80 to R-136; P-81 to R-136; P-82 to R-136; C-
 83 to R-136; W-84 to R-136; K-85 to R-136; V-86 to R-136; A-87 to R-136; Q-88 to
 10 R-136; V-89 to R-136; D-90 to R-136; S-91 to R-136; L-92 to R-136; K-93 to R-136;
 D-94 to R-136; K-95 to R-136; A-96 to R-136; R-97 to R-136; K-98 to R-136; L-99
 to R-136; Y-100 to R-136; T-101 to R-136; I-102 to R-136; M-103 to R-136; N-104
 to R-136; S-105 to R-136; F-106 to R-136; C-107 to R-136; R-108 to R-136; R-109
 to R-136; D-110 to R-136; L-111 to R-136; V-112 to R-136; F-113 to R-136; L-114
 15 to R-136; L-115 to R-136; D-116 to R-136; D-117 to R-136; C-118 to R-136; N-119
 to R-136; A-120 to R-136; L-121 to R-136; E-122 to R-136; Y-123 to R-136; P-124
 to R-136; I-125 to R-136; P-126 to R-136; V-127 to R-136; T-128 to R-136; T-129 to
 R-136; V-130 to R-136; and L-131 to R-136 of SEQ ID NO:310. Polypeptides
 encoded by these polynucleotides are also encompassed by the invention. Moreover,
 20 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides, or the complement thereof are encompassed by the invention.
 25 Antibodies that bind polypeptides of the invention are also encompassed by the
 invention. Polynucleotides encoding these polypeptides are also encompassed by the
 invention.

Also as mentioned above, even if deletion of one or more amino acids from
 the C-terminus of a protein results in modification or loss of one or more biological
 30 functions of the protein (e.g., ability to induce hematopoiesis), other functional
 activities (e.g., biological activities, ability to multimerize, ability to bind receptors,
 ability to activate receptors, ability to bind and block receptor activation, ability to

inhibit receptor activation without binding (e.g., as a dominant negative inhibitor of oligomeric complexes), ability to generate antibodies, ability to bind antibodies) may still be retained. For example the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxyl terminus of the amino acid sequence of the polypeptide shown in Figures 5A-5B (SEQ ID NO:310), as described by the general formula 1-n, where n is an integer from 6 to 135, where n corresponds to the position of the amino acid residue identified in SEQ ID NO:310. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: M-1 to Q-135; M-1 to R-134; M-1 to D-133; M-1 to P-132; M-1 to L-131; M-1 to V-130; M-1 to T-129; M-1 to T-128; M-1 to V-127; M-1 to P-126; M-1 to I-125; M-1 to P-124; M-1 to Y-123; M-1 to E-122; M-1 to L-121; M-1 to A-120; M-1 to N-119; M-1 to C-118; M-1 to D-117; M-1 to D-116; M-1 to L-115; M-1 to L-114; M-1 to F-113; M-1 to V-112; M-1 to L-111; M-1 to D-110; M-1 to R-109; M-1 to R-108; M-1 to C-107; M-1 to F-106; M-1 to S-105; M-1 to N-104; M-1 to M-103; M-1 to I-102; M-1 to T-101; M-1 to Y-100; M-1 to L-99; M-1 to K-98; M-1 to R-97; M-1 to A-96; M-1 to K-95; M-1 to D-94; M-1 to K-93; M-1 to L-92; M-1 to S-91; M-1 to D-90; M-1 to V-89; M-1 to Q-88; M-1 to A-87; M-1 to V-86; M-1 to K-85; M-1 to W-84; M-1 to C-83; M-1 to P-82; M-1 to P-81; M-1 to S-80; M-1 to A-79; M-1 to V-78; M-1 to F-77; M-1 to D-76; M-1 to R-75; M-1 to L-74; M-1 to K-73; M-1 to D-72; M-1 to L-71; M-1 to V-70; M-1 to C-69; M-1 to Y-68; M-1 to N-67; M-1 to H-66; M-1 to I-65; M-1 to D-64; M-1 to L-63; M-1 to Y-62; M-1 to L-61; M-1 to R-60; M-1 to P-59; M-1 to L-58;

M-1 to Y-57; M-1 to R-56; M-1 to V-55; M-1 to C-54; M-1 to P-53; M-1 to E-52; M-1 to S-51; M-1 to P-50; M-1 to E-49; M-1 to S-48; M-1 to V-47; M-1 to Q-46; M-1 to L-45; M-1 to L-44; M-1 to N-43; M-1 to F-42; M-1 to D-41; M-1 to R-40; M-1 to T-39; M-1 to I-38; M-1 to E-37; M-1 to Q-36; M-1 to S-35; M-1 to L-34; M-1 to A-33; M-1 to R-32; M-1 to M-31; M-1 to R-30; M-1 to S-29; M-1 to Y-28; M-1 to C-27; M-1 to T-26; M-1 to P-25; M-1 to P-24; M-1 to T-23; M-1 to P-22; M-1 to R-21; M-1 to A-20; M-1 to A-19; M-1 to P-18; M-1 to A-17; M-1 to G-16; M-1 to A-15; M-1 to L-14; M-1 to L-13; M-1 to L-12; M-1 to L-11; M-1 to L-10; M-1 to V-9; M-1 to P-8; and M-1 to L-7 of SEQ ID NO:310. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:310, where n and m are integers as described above. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: M-1 to A-15; R-2 to G-16; T-3 to A-17; P-4 to P-18; G-5 to A-19; P-6 to A-20; L-7 to R-21; P-8 to P-22; V-9 to T-23; L-10 to P-24; L-11 to P-25; L-12 to T-26; L-13 to C-27; L-14 to Y-28; A-15 to S-29; G-16 to R-30; A-17 to M-31; P-18 to R-32; A-19 to A-33; A-20 to L-34; R-21 to S-35; P-22 to Q-36; T-23 to E-37; P-24 to I-38; P-25 to T-39; T-26 to R-40; C-27 to D-41; Y-28 to F-42; S-29 to N-43; R-30 to L-44; M-31 to L-45; R-32 to Q-46; A-33 to V-47; L-34 to S-48; S-35 to E-49; Q-36 to P-50; E-37 to S-51; I-38 to E-52; T-39 to P-53; R-40 to C-54; D-41 to V-55; F-42 to R-56; N-43 to Y-57; L-44 to L-58; L-45 to P-59; Q-

46 to R-60; V-47 to L-61; S-48 to Y-62; E-49 to L-63; P-50 to D-64; S-51 to I-65;
E-52 to H-66; P-53 to N-67; C-54 to Y-68; V-55 to C-69; R-56 to V-70; Y-57 to L-
71; L-58 to D-72; P-59 to K-73; R-60 to L-74; L-61 to R-75; Y-62 to D-76; L-63 to
F-77; D-64 to V-78; I-65 to A-79; H-66 to S-80; N-67 to P-81; Y-68 to P-82; C-69
5 to C-83; V-70 to W-84; L-71 to K-85; D-72 to V-86; K-73 to A-87; L-74 to Q-88;
R-75 to V-89; D-76 to D-90; F-77 to S-91; V-78 to L-92; A-79 to K-93; S-80 to D-
94; P-81 to K-95; P-82 to A-96; C-83 to R-97; W-84 to K-98; K-85 to L-99; V-86 to
Y-100; A-87 to T-101; Q-88 to I-102; V-89 to M-103; D-90 to N-104; S-91 to S-
105; L-92 to F-106; K-93 to C-107; D-94 to R-108; K-95 to R-109; A-96 to D-110;
10 R-97 to L-111; K-98 to V-112; L-99 to F-113; Y-100 to L-114; T-101 to L-115; I-
102 to D-116; M-103 to D-117; N-104 to C-118; S-105 to N-119; F-106 to A-120;
C-107 to L-121; R-108 to E-122; R-109 to Y-123; D-110 to P-124; L-111 to I-125;
V-112 to P-126; F-113 to V-127; L-114 to T-128; L-115 to T-129; D-116 to V-130;
D-117 to L-131; C-118 to P-132; N-119 to D-133; A-120 to R-134; L-121 to Q-135;
15 and E-122 to R-136 of SEQ ID NO:310. Polynucleotides encoding these
polypeptides are also encompassed by the invention. Moreover, fragments and
variants of these polypeptides (such as, for example, fragments as described herein,
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
these polypeptides and polypeptides encoded by the polynucleotide which
20 hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides, or the complement thereof are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
invention. Polynucleotides encoding these polypeptides are also encompassed by
the invention.

25 The present invention is also directed to proteins containing polypeptides at
least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a
polypeptide sequence set forth herein as m-n. In preferred embodiments, the
application is directed to proteins containing polypeptides at least 80%, 85%, 90%,
95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid
30 sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides
encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 97975 (deposited April 4, 1997) and ATCC Deposit No. 209081 (deposited May 29, 1997), where this portion excludes any integer of
5 amino acid residues from 1 to about 606 (end of protein minus six) amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 97975 and 209081, or any integer of amino acid residues from 6 to about 612 amino acids from the carboxyl terminus, or any combination of the above amino terminal and carboxyl terminal deletions, of the
10 complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 97975 and 209081. Polypeptides encoded by these polynucleotides also are encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
15 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis for chromosome 4.

This gene is expressed primarily in fetal liver and fetal spleen.

25 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immunological, developmental, and/or hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
30 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels

may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, hepatic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. For example, polynucleotides and polypeptides of the invention, polynucleotide and polypeptide fragments, and polynucleotide and polypeptide variants, and antibodies directed to these polypeptides are useful for identifying, selecting, targeting and/or stimulating proliferation of hematopoietic stem cells (a.k.a., hematopoietic progenitor cells).

Cytokines typically exert their respective biochemical and physiological effects by binding to specific receptor molecules. Receptor binding then stimulates specific signal transduction pathways (Kishimoto, T., *et al.*, *Cell* 76:253-262 (1994)). The specific interactions of cytokines with their receptors are often the primary regulators of a wide variety of cellular processes including activation, proliferation, and differentiation (Arai, K. -I, *et al.*, *Ann. Rev. Biochem.* 59:783-836 (1990); Paul, W. E. and Seder, R. A., *Cell* 76:241-251 (1994)).

The polynucleotides and polypeptides of this invention may be useful for the diagnosis and treatment of a variety of immune system and hematopoietic disorders, pathologies, and/or deficiencies. For example, this gene and/or gene product may play a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Furthermore, polypeptides of this invention may be involved in the regulation of cytokine production, antigen presentation, or other processes useful for treatment of cancer, particularly leukemia (e.g., by boosting immune responses, suppressing hyperproliferative activity, or enhancing recovery of healthy hematopoietic cell populations during or following chemotherapy). Moreover, the polynucleotides and polypeptides of this invention, as well as antibodies against the polypeptides of this invention, may be useful for treating immunological and hematopoietic disorders; such as for examples, arthritis, asthma, immunodeficiency diseases (e.g. AIDS), leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia,

neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the polypeptide of this invention represents a
5 secreted factor that is likely to have activity in stimulating the differentiation of blood cells, or recruiting immune and hematopoietic cells to sites of injury. Thus, this polypeptide is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of
10 various cell types.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 310 as residues: Met-1 to Leu-7, Pro-18 to Cys-27, Ser-29 to Ser-35, Glu-37 to Asp-41, Gln-46 to Cys-54, Asp-72 to Val-78, Pro-81 to Trp-84, Ser-91 to Lys-98, Asn-104 to Leu-
15 111, Asp-116 to Leu-121, and Val-130 to Arg-136. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution of this gene in fetal liver and spleen indicates that the gene could be important for the treatment or detection of immune or hematopoietic
20 disorders including arthritis, leukemia, and immunodeficiency diseases. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture,
25 bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of
30 various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and

treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 982 of SEQ ID NO:72, b is an integer of 15 to 996, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene shares homology with human serum amyloid protein (See Genbank Accession No. W13671).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

ALTRIPPGDWVINVTAVSFAGKTTARFFHSSPPSLGDQARTDPGHQRRD (SEQ ID NO:711), SMLLLFPLQERPQQDSFIRLLLAWGTRLELTLDIKGGI (SEQ ID NO:712),

TGLWADGFSSHIIPPLMSRVSSSLVPQARRRRMKESCCGLSCKGNSSNIDYPV
TGRNSCERAPLCAFALHFQERTXITGXGEDPGPFQSGRVTASRXTLACSHV

AMTPAGCXQALGTPSSYCVRKAPRA (SEQ ID NO:713), and/or

QARRRRMKESCCGLSCKGNSSNIDYPVT (SEQ ID NO:714). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as

described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in fetal liver and spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immune, and/or developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in fetal liver-spleen indicates that the gene is important for the treatment or detection of immune or hematopoietic disorders including arthritis, leukemia, and immunodeficiency diseases. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene

product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency, etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:73, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 64

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: LWRSSGVER (SEQ ID NO:715). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide

encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome

- 5 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed specifically in the brain.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
- 10 and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly neurodegenerative disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
- 15 neurological systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression
- 20 level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution in brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis,
- 25 demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In
- 30 addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility
5 as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1055 of SEQ ID NO:74, b is an integer of 15 to 1069, where both a and b correspond to the positions of nucleotide
15 residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 65

20 This gene shares homology with a yeast protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
LQEVNITLPENSVWYERYKFDIPVFHL (SEQ ID NO:716). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein,
25 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are
30 also encompassed by the invention. (See Genbank Accession No. 1332638).

This gene is expressed primarily in fetal tissue (fetus and fetal liver).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic, developmental, immune, and/or hematopoietic disorders, including cancers (e.g. hepatoblastoma). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, developmental, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 313 as residues: Asn-72 to Glu-77.

The tissue distribution in fetal liver indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed

progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 817 of SEQ ID NO:75, b is an integer of 15 to 831, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 66

This gene has homology with a B-cell surface antigen which may indicate that
20 this gene plays a role in the immune response, including, but not limited to disorders and infections of the immune system.

Preferred polynucleotide fragments comprise the following sequence:
GTAGCATGTAGCCAGTCGAATAACNTATAAGGACAAAGTGGAGTCCACGC
GTGCGCCGTCTAGACTAGTGGATCCCCCGGCTGCAGGATTCGGCACGAG
25 (SEQ ID NO:718). Also preferred are polypeptides comprising polypeptide fragments encoded by these polynucleotide fragments.

This gene shares homology with an interferon-gamma receptor (See Genbank Accession No.T94535).

In specific embodiments, polypeptides of the invention comprise, or
30 alternatively consists of, an amino acid sequence selected from the group:
MQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGGRFPKTCRAISQNLVFKY
KTFPCVRYMQPHRSSLC LHFTSYVFILSTWGLRTYSTDLKKKKKNSRGGPVP

IRPKS (SEQ ID NO:717),
MQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGGRRFPKTCRAISQNLVFK
(SEQ ID NO:719),
PVRYMQPHRSSLC LHFTSYVFILSTWGSLRTYSTDLKKKKKNSRGGPVPIRPK
5 S (SEQ ID NO:720),
GEEQRDCSLGWRGVGMRATHCQAARMFVLFSLPKYAGL (SEQ ID NO:721),
TSGSPGCRIRHELPGEEQRDCSLGWRGVGMRATHCQAAR (SEQ ID NO:722),
EPPIAKQQECSCFFPFQNMQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGGRR
RFPKTCRAISQNLVFKYKTFCPVRYMQPHRSSLC LHFTSYVFILSTWGSLRTY
10 STDLKKKKKNSRGGPVPIRPKS (SEQ ID NO:723), and/or
QFRACLLCLCFSCPCSPGGPRWNSRQGGRRF (SEQ ID NO:724). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
15 which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in T-cells and gall bladder.

20 Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
immunological disorders and conditions (immunodeficiencies, cancer, leukemia,
hematopoiesis), in addition to metabolic, gastrointestinal, and/or digestive disorders.
25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in
providing immunological probes for differential identification of the tissue(s) or cell
type(s). For a number of disorders of the above tissues or cells, particularly of the
immune and digestive systems, expression of this gene at significantly higher or
lower levels may be routinely detected in certain tissues or cell types (e.g., immune,
30 hematopoietic, metabolic, gastrointestinal, digestive, and cancerous and wounded
tissues) or bodily fluids (e.g., lymph, serum, bile, plasma, urine, synovial fluid and
spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 314 as residues: Thr-41 to Gly-52.

5 The tissue distribution in T-cells indicates that the protein product of this gene is useful for the treatment and diagnosis of immune disorders including: leukemias, lymphomas, auto-immune disorders, immunosuppressive (transplantation) and immunodeficiencies (e.g. AIDS), inflammation and hematopoietic disorders. Moreover, the expression of this gene in gall bladder would suggest a possible role
10 for this gene product in digestive disorders, particularly of the pancreas or liver. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
15 related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
20 formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:76, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 67

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
NQFTSCILFCDGGHWRELLFQSI (SEQ ID NO:725),
30 AMSSKLLNLLALLQYSVHDHCHPRRLKRGARATLRHKGWGPSSLRGCESF
QIVLIGWGPD LAVGFGRGKLLSRSLPVRHGGVSEFCLPHRDVVRLEKVKK
(SEQ ID NO:726), and/or GPSSLRGCESFQIVLIGWGPD LAVGFGRGKLLS (SEQ

ID NO:727). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in a variety of fetal and developmental tissues (e.g. fetal spleen, infant brain).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, immune or neurological abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing immune and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, hepatic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 315 as residues: Ser-38 to Ser-43.

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful for developmental abnormalities or fetal deficiencies. The detection in infant brain would suggest a role in neurological disorders (both developmental and neurodegenerative conditions of the brain and nervous system, behavioral disorders,

depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia). In addition, the detection in spleen would similarly suggest a role in the detection and treatment of immune disorders (e.g. immunodeficiency, inflammation, cancer, wound healing, tissue repair, hematopoiesis). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1260 of SEQ ID NO:77, b is an integer of 15 to 1274, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 68

20

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
TRKNIDFXETEKYYLFSFSNNVSFKNFWLKYN (SEQ ID NO:728). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

30

This gene is expressed primarily in spleen, T-cells, and fetal heart.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological or hematopoietic deficiencies or disorders, including AIDS and cardiovascular or developmental conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and cardiovascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, cardiovascular, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen and T-cells indicates that the protein product of this gene is useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, autoimmune disorders, immunodeficiencies (e.g. AIDS), immunosuppressive conditions (transplantation) and hematopoietic disorders. Moreover, the expression in fetal heart indicates that the protein product of this gene is useful for the treatment and diagnosis of cardiovascular disorders (e.g. heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1119 of SEQ ID NO:78, b is an

integer of 15 to 1133, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 69

This gene shares homology with a human collagen protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 10 MPRKTSKCRQLLCSGASRNADTAARQSTCSSHRPPGKIPSLGPRRXPGCXSV
SSRGEQSTGSPAAPRCGRRDAHRGLPGGAAMTPGDTWASFNPRAGHSKSQ
EGQESSGASRQDRHPVSHWVERQREAWGAPRSSSAGGVKVAATTEREPEFKI
KTGKA (SEQ ID NO:729),
CSGASRNADTAARQSTCSSHRPPGKIPSLGPRRXPGCXSVSSRGEQSTGSPA
15 APRCGRRDAHRGLPGGAAMTPGDTWASFNPRAGHS (SEQ ID NO:730),
QGEGQESSGASRQDRHPVSHWVERQREAWGAPRSSSAGGVKVAATTEREPE
FKIKTGKA (SEQ ID NO:731),
IRHEGKRMLNESRKPLSFASRLSSLYFKLGFPPFCGRSNLYSTCTAAPGGSPGLP
LPFYVPADG (SEQ ID NO:732),
20 TRAESLFPLLHAFPVFILNSGSLSVVAATFTPPALLLLGAPQASLCLSTQWLTG
CLSCLDAPLLSCPSWLLLCALGLKLAHVSPGVMAAPPGRPLCASRLPHLGA
AGEPVLCSPRLLGTELQPGXLRGPRLGILPGGRWEEQVLCLAAVSAFLDAPEH
RSCRHFEVFLGMCQIT (SEQ ID NO:733),
PALGLKLAHVSPGVMAAPPGRPLCASRLP (SEQ ID NO:734),
25 GGRWEEQVLCLAAVSAFLDAPEHR (SEQ ID NO:735),
SWPMCPPEWLLLLGGLCVRHVFHTWGQLASPCSVPLGCLAQSCSLGXSVDP
DWGFCQGGDGRSRCFAWRLCLHFWTPQSTEVAGTLRSSACARLHE (SEQ
ID NO:736), and/or GDGRSRCFAWRLCLHFWTPQSTEVAGTLR (SEQ ID
NO:737). Moreover, fragments and variants of these polypeptides (such as, for
30 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,
96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by
the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal heart.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular or developmental disorders, particularly vascular conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in
10 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, developmental, skeletal, vascular, and cancerous and wounded tissues) or bodily
15 fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
20 NO: 317 as residues: Pro-32 to Ser-39.

The tissue distribution in fetal heart indicates that the protein product of this gene is useful for the treatment and diagnosis of cardiovascular disorders (e.g. heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis), in addition to vascular disorders, such as microvascular disease. Expression within fetal tissue
25 indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer
30 therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 647 of SEQ ID NO:79, b is an integer of 15 to 661, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

The translation product of this gene shares sequence homology with a chicken single-strand DNA-binding protein. The promoter region of the chicken alpha2(I) collagen gene contains a pyrimidine-rich element that is well conserved in different mammalian species. This sequence can also form an unusual DNA structure as shown by its sensitivity to SI nuclease in vitro and it lies in a region that is DNase I-hypersensitive only when this promoter is active. The high affinity of this protein for this conserved pyrimidine-rich region indicates that it might be involved in the transcriptional regulation of the alpha2(I) collagen gene.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MSPRYPGGPRPPLRIPNQALGGVPGSQPLLPSGMDPTRQQGHPNMGGPMQR
 MTPPRGMVPLGPQNYGGAMRPLNALGGPGMPGMNMGPGGGRPWPNPNTN
 ANSIPYSSASPGNYVGPPGGGGPPGTPIMPSPADSTNSGDNMYTLMNAVPPGP
 NRPNFPMGPGSDGPMGGLGGMESHMNGSLGSGDMDSISKNSPNNMSLSNQ
 PGTPRDDGEMGGNFLNPFQSESYSMTMSV (SEQ ID NO:738),
 MSPRYPGGPRPPLRIPNQALGGVPGSQPLLPSGMDPTRQQGHPNMGGPMQR
 MTPPRGMVPLGPQNYGGAMRPLNALGGPGMPGMNMGPGGGRPWPNPNTN
 ANSIPYSSASPGNY (SEQ ID NO:739),

LNALGGPGMPGMNMGPGGGRWPNPNTNANSIPYSSASPGNYVGPPGGGGPP
GTPIMPSPADSTNSGDNMYTLMNAVPPGPN (SEQ ID NO:740),
GPMGGLGGMESHHMNGSLGSGDMDSISKNSPNNMSLSNQPGTTPRDDGEMG
GNFLNPFQSESYSPSMTMSV (SEQ ID NO:741), TCEHSSEAKAFHDY (SEQ ID
5 NO:742), and/or RRETCEHSSEAKAFHDYPF (SEQ ID NO:743),. Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
10 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention. (See Genbank Accession
No. 1562534)

This gene is expressed primarily in placenta, and to a lesser extent, in fetal
15 heart.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
developmental abnormalities, fetal deficiencies, and particularly of the cardiovascular
20 system and/or vascular conditions. Similarly, polypeptides and antibodies directed to
these polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the reproductive system, expression of this gene at
significantly higher or lower levels may be routinely detected in certain tissues or cell
25 types (e.g., developmental, vascular, cardiovascular, reproductive, and cancerous and
wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine,
synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
the expression level in healthy tissue or bodily fluid from an individual not having the
30 disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 318 as residues: Met-1 to Leu-13, Gly-33 to Gly-46, Pro-48 to Gly-57, Pro-63 to

Gly-68, Pro-89 to Asn-102, Ser-108 to Asn-113, Pro-118 to Pro-124, Pro-132 to Asn-141, Pro-151 to Asn-157, Ile-191 to Met-199, Ser-202 to Gly-215, Phe-222 to Pro-229.

The tissue distribution in fetal heart and placenta indicates that the protein product of this gene is useful for the detection and treatment of developmental abnormalities or fetal deficiencies, ovarian and other endometrial cancers, reproductive dysfunction, cardiovascular disorders, and pre-natal disorders, in particular vascular disorders, which include, but are not limited to, stroke, angina, microvascular disease, atherosclerosis, embolism, and aneurysm. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1364 of SEQ ID NO:80, b is an integer of 15 to 1378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: TITLFQSAWCFFSKYCTDFT (SEQ ID NO:744), VRGCEGGGGGIWGGWWPGQQMAPPWLSCPHRQFPHFHSGRQRRQSDLLK EELPQPSGAAGRASGNKPYTPPPASNSLTLRLLSFRFNAFNRSHPQPSLNKYD RQ (SEQ ID NO:745), PWLSCPHRQFPHFHSGRQRRQSDLL (SEQ ID NO:746), and/or RLLSFRFNAFNRSHPQPSLN (SEQ ID NO:747). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in fetal liver, and to a lesser extent, in the breast and testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic disorders (including hepatoblastomas), hematopoietic, immune, and/or reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, hepatic, reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). The expression in testes and breast indicates that the protein product of this gene is useful for the

detection and treatment of endocrine and reproductive disorders (e.g. sperm maturation, milk production, testicular and breast cancers). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1426 of SEQ ID NO:81, b is an integer of 15 to 1440, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 72

In specific embodiments, polypeptides of the invention comprise, or
20 alternatively consists of, an amino acid sequence selected from the group:
RDSSLWAAALSFRQQCSSLASCLVSMYSRPGRQHRAGAGSQTEQCWGRK
VDAVV (SEQ ID NO:748), CLVSMYSRPGRQHRAGAGSQTEQCW (SEQ ID
NO:749),
PEHGFSSCDFWEGAPSSGPKEGGRSPPQLACVWGMNLSSPPCLALLTNRACL
25 AVNWHRVTLFPGIQVCNQNTGEEKLQDPCPHLSS (SEQ ID NO:750),
RSPPQLACVWGMNLSSPPCLALLTNRACLA (SEQ ID NO:751),
CERDSETSSIAMTCIKHKPPKQKKRLSLLPGFRSALPRVCRCHMITVQREAFRT
HTGCSTSVHLPSRGGFLPDF (SEQ ID NO:752), and/or
KKRLSLLPGFRSALPRVCRCHMITVQRE (SEQ ID NO:753).

30 Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the

polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

 This gene is expressed primarily in smooth muscle, and to a lesser extent, in brain.

10 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular and neurological disorders, particularly embolism, atherosclerosis, stroke, aneurysm, and microvascular disease. Similarly, polypeptides and antibodies
15 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, vascular, endothelial,
20 smooth muscle, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in brain and smooth muscle indicates that the protein product of this gene is useful for the detection and treatment of restenosis, atherosclerosis, stroke, angina, thrombosis, wound healing and other conditions of heart disease. Moreover, the protein product of this gene is useful for the detection and treatment of developmental, degenerative and behavioral conditions of the brain
30 and nervous system (e.g. schizophrenia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and

sleep disorders). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1367 of SEQ ID NO:82, b is an integer of 15 to 1381, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 73

This gene shares homology with human stromalin-2, which is believed to play an integral role in modulating cellular function of hematopoietic cells and tissues, and may possibly serve as a tumor suppressor.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

QAFVLLSDLLIFSPQMIVGGRDFLRPLVFFPEATLQSELASFLMDHVFIQPGD
 LGSGA (SEQ ID NO:754),
 ACSYLLCNPEFTFFSRADFARSQVLDLLTDRFQQELEELLQVG (SEQ ID
 NO:755), QKQLSSLRDRMVAFCCLCQSCSDVDTEIQEQVST (SEQ ID
 NO:756), QVILPALTLVYFSILWTLTHISKSDAS (SEQ ID NO:757),
 STHDLTRWELYEPCCQLLQKAVDTGXVPHQV (SEQ ID NO:758),
 TSFLFPLQAFVLLSDLLIFSPQMIVGGRDFLRPLVFFPEATLQSELASFLMDH
 VFIQ PGDLGSGA (SEQ ID NO:759),
 GWGACSYLLCNPEFTFFSRADFARSQVLDLLTDRFQQELEELLQVGAGAGQ
 WDTPNKGGRGCKTGDVD (SEQ ID NO:760),
 VWVLDGIMGTEESVSSFFPKPLCPQKQLSSLRDRMVAFCCLCQSCSDVDTE

IQEQVSTDSSGSNKASIPAPIPRRN (SEQ ID NO:761),
 NASLPSTSEWLSSSSPSRFYWCLWSWFPLFFSSITFPFLPQSTHDLTRWELYEP
 CCQLLQKAVDGTGXVPHQVSGQARDGLGAGGLXFKDLRSRWPLGVSSLSAW
 SGQSEEDQVGGGHLLHSSLRRWTLPGSSWISWKPRIILRDSRRRRVN (SEQ
 5 ID NO:762), VLGEMLLWIFFPSQSSFLDEDEVYNLAATLKRLSAFYK (SEQ ID
 NO:763), PKPHFSNPLLLQVILPALTLVYFSILWTLTHISKSDASPGECGS (SEQ
 ID NO:764), and/or HCQFLLG (SEQ ID NO:765). Moreover, fragments and
 variants of these polypeptides (such as, for example, fragments as described herein,
 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
 10 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,
 under stringent conditions, to the polynucleotide encoding these polypeptides) are
 encompassed by the invention. Antibodies that bind polypeptides of the invention are
 also encompassed by the invention. Polynucleotides encoding these polypeptides are
 also encompassed by the invention. (See Genbank Accession No.R65208)

15 The gene encoding the disclosed cDNA is believed to reside on chromosome
 7. Accordingly, polynucleotides related to this invention are useful as a marker in
 linkage analysis for chromosome 7.

This gene is expressed primarily in the brain (infant brain, adult brain,
 pituitary, cerebellum, hippocampus, schizophrenic hypothalamus, amygdala).

20 Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 developmental disorders and neurodegenerative diseases of the brain and nervous
 system, in addition to immune or hematopoietic disorders. Similarly, polypeptides
 25 and antibodies directed to these polypeptides are useful in providing immunological
 probes for differential identification of the tissue(s) or cell type(s). For a number of
 disorders of the above tissues or cells, particularly of the central nervous system,
 expression of this gene at significantly higher or lower levels may be routinely
 detected in certain tissues or cell types (e.g., neural, developmental, immune,
 30 hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,
 amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue
 or cell sample taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 321 as residues: Thr-25 to Lys-36, Lys-55 to Ser-63.

5 The tissue distribution primarily in brain, combined with the homology to the highly conserved SA-1 and SA-2 proteins, indicates that the protein product of this gene is useful for the detection and treatment of developmental, degenerative and behavioral conditions of the brain and nervous system (e.g. schizophrenia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and sleep disorders). Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1692 of SEQ ID NO:83, b is an integer of 15 to 1706, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 74

5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
EFGTSLVALELHELLYHWETRAQPSLILYVSDLRWMEFRTSCLLFDFVLFLFLE
(SEQ ID NO:766),
TKPGMVGHVPIVPATKXAEAGGSPEPGSSTLQWPMITPCTPSWATEPDHVSE
10 DE (SEQ ID NO:767), and/or LLYHWETRAQPSLILYVSDLRWMEFRTSC (SEQ ID NO:768).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
15 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the hypothalamus of a human suffering
20 from schizophrenia.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the CNS, particularly schizophrenia. Similarly, polypeptides and
25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, such as schizophrenia expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded
30 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 322 as residues: Gly-38 to Ala-44.

5 The tissue distribution in the hypothalamus indicates that the protein products of this gene are useful for the study, diagnosis and treatment of schizophrenia and other disorders involving the CNS. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's
10 Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors,
15 including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role
20 in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

 Many polynucleotide sequences, such as EST sequences, are publicly
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 559 of SEQ ID NO:84, b is an

integer of 15 to 573, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 75

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- LAVSTSFICCADISTALPLGSSRPAPAPRHREHEHGHQARPPRLXTSLMPLST
 10 PAAAQLLWTQLTPMGGRPGGRHSPPTLHTGPRALPPGPPHPSLHVAALSLLR
 (SEQ ID NO:769),
 APAVPHQPPGTESTSMGTPGLPGCSXRPLCHYQHQLXPSYFGHSSPPWG
 AVLVGVTTPHPRCTPAPGPCRLGLHHPCTWQLCLC (SEQ ID NO:770),
 CADISTALPLGSSRPAPAPRHREHEHGH (SEQ ID NO:771),
 15 WTQLTPMGGRPGGRHSPPTLHTGPR (SEQ ID NO:772), and/or HQPPGTEST
 SMGTPGLPGC (SEQ ID NO:773). Moreover, fragments and variants of these
 polypeptides (such as, for example, fragments as described herein, polypeptides at
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent
 20 conditions, to the polynucleotide encoding these polypeptides) are encompassed by
 the invention. Antibodies that bind polypeptides of the invention are also
 encompassed by the invention. Polynucleotides encoding these polypeptides are also
 encompassed by the invention.

- 25 This gene is expressed primarily in endometrial tumors, and to a lesser extent,
 in amniotic cells.

- Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 reproductive, developmental, and immune disorders, particularly cancers of those
 30 systems. Similarly, polypeptides and antibodies directed to these polypeptides are
 useful in providing immunological probes for differential identification of the
 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 323 as residues: Ser-3 to Arg-9.

The tissue distribution in endometrium and amniotic cells indicates that the protein products of this gene are useful for the study and treatment of developmental, reproductive, and immune disorders, particularly cancers of those systems. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 670 of SEQ ID NO:85, b is an integer of 15 to 684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 76

In specific embodiments, polypeptides of the invention comprise, or
 5 alternatively consists of, an amino acid sequence selected from the group:
 SRGSLPPHLP HRVVVRVHRGAKSLKALRQYIGAAHLQLPWDGKDPARPLGI
 TLCLQMEIQVLG (SEQ ID NO:774),
 CCSFGFYVMVGSDTAEKQGPIPGSQTQEGPWLSRHTHSPRAVPESSTAPAQ
 PLLLPAPQARRWASNANGWGWDHQREGQANYPYSARPAPHNLHPQYLN
 10 LHLQTQCYAQGSGWVLPPIG QLKVGGPYILPEGLQGLCSSVHPHNNPVR
 (SEQ ID NO:775), HRGAKSLKALRQYIGAAHLQLPWDG (SEQ ID NO:776),
 PAPQARRWASNANGWGWDHQR (SEQ ID NO:777), and/or
 HPQYLNHLHLQTQCYAQGSGWVLP (SEQ ID NO:778).

Moreover, fragments and variants of these polypeptides (such as, for example,
 15 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.
 20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
 22. Accordingly, polynucleotides related to this invention are useful as a marker in
 linkage analysis for chromosome 22.

This gene is expressed primarily in kidney cortex, and to a lesser extent, in
 25 early stage human brain.

Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 renal disorders such as renal cancer, developmental, or neural disorders, particularly
 30 cancers. Similarly, polypeptides and antibodies directed to these polypeptides are
 useful in providing immunological probes for differential identification of the
 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the kidney expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, neural, renal, urogenital, endothelial, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or
5 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 324 as residues: Gly-38 to Gly-45, Gly-47 to Gly-52, Pro-92 to Lys-110.

10 The tissue distribution in kidney cortex indicates that the protein products of this gene are useful for the study, treatment and diagnosis of renal diseases, including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms
15 Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Moreover, the expression within human brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease,
20 Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in
25 feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment
30 and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, the protein product may also show utility in the treatment and/or prevention of a variety

of vascular disorders, particularly embolism, aneurysm, stroke, atherosclerosis, or microvascular disease. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1022 of SEQ ID NO:86, b is an integer of 15 to 1036, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 77

20 In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:
TNGIMQYVTFVCVWLILFSIMFLRFIQAVACISTSFLFLAEYYSIWYIYHNSFTYSS
FVSAVWLL (SEQ ID NO:779), YNFMFNFSKNCQKVFHSGCIYIPTGNVQGFLF
FHILALTNT SFXXXFCFFIATLVDVKWHLIVLICISLMTNDIILFLCAYGSK
25 VFPWRNPSSPLPFQNLVICLLLSF KKFVPGAVAHL (SEQ ID NO:780),
CVTQARVQWRDLGSLQPPPPGFKRFSCLSLLSRXDYMHLPPRPANFCIFSKM
GFHHVGQAGLEV LXSSDL PALASQSAXITGEPLRLARIS (SEQ ID NO:781),
LILFSIMFLRFIQAVACISTSFLF (SEQ ID NO:783), and/or LPPRPANFCIFSK
MGFHHVGQAGLE (SEQ ID NO:782). Moreover, fragments and variants of these
30 polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent

conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in kidney medulla.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic and renal disorders. Similarly, polypeptides and antibodies directed to
10 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, urogenital, endocrine, and cancerous and wounded
15 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in kidney tissue indicates that the protein products of
20 this gene are useful for study, treatment and diagnosis of metabolic and renal diseases and disorders. Moreover, this gene or gene product could be used in the treatment and/or detection renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms
25 Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 894 of SEQ ID NO:87, b is an integer of 15 to 908, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 78

10

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

ALVPSPQQILPSCFSLMWQVTTKSALVFFKCIYIPFLSAPSLPRLNCLIFCSLD
VQSQLVFLSSPPVAGVLFFLLSPLGSKSCSTVEX (SEQ ID NO:784), and/or

15 APSLPRLNCLIFCSLDVQSQLVFLS (SEQ ID NO:785). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

20

This gene is expressed in chronic synovitis and microvascular endothelium.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal or vascular disorders, such as arthritis and atherosclerosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).

25

30 For a number of disorders of the above tissues or cells, particularly of the vascular and skeletal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, synovium,

endothelial cells, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in synovium and microvascular endothelium indicates that the protein products of this gene are useful for study, diagnosis and treatment of arthritic and other inflammatory diseases as well as cardiovascular diseases. Moreover, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). In addition, the protein would also be useful in the treatment and/or prevention of a variety of vascular disorders, which include, but are not limited to, microvascular disease, embolism, thrombosis, aneurysm, stroke, or atherosclerosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 641 of SEQ ID NO:88, b is an integer of 15 to 655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 79

5 In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: SSPSRVRLRHTPG (SEQ ID NO:786), and/or
SNTNYCFMFFYFPVKVLVPFKNCYILSLILPCCICGHQFPRXQACTFCLHTLG
GFSFSXLFLVLLSFYVQTGFSV (SEQ ID NO:787). Moreover, fragments and
10 variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are
15 also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

 This gene is expressed in resting T-cells and activated monocytes.

 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
20 and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at
25 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily
30 fluid from an individual not having the disorder.

 The tissue distribution in T-cells and monocytes indicates that the protein products of this gene are useful for the study and treatment of immune diseases such

as inflammatory conditions. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1088 of SEQ ID NO:89, b is an integer of 15 to 1102, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 80

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

GTSRHGQRPIAPGTPWQREPRVEVMDPAGGPRGVLPRPCRXLVLLNPRGGKG
KALQLFRSHVQPLLAEBEISFTLMLTERRNHARELVRSEELGRWXALVVMXG

5 D GLMHEVVNGLHGAA (SEQ ID NO:788), and/or

RPIAPGTPWQREPRVEVMDPAGGP (SEQ ID NO:789). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
15 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

This gene is expressed in a variety of immune system tissues, e.g., neutrophils, T-cells, and TNF induced epithelial and endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infectious and immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
25 disorders of the above tissues or cells, particularly of the immune and vascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an
30 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 328 as residues: Met-1 to Trp-6.

The tissue distribution in immune tissues and cells indicates that the protein products of this gene are useful for the study and treatment of infectious diseases, immune and vascular disorders. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1519 of SEQ ID NO:90, b is an integer of 15 to 1533, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 81

5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: ASGPLMGXAVLKIFE (SEQ ID NO:790). Polynucleotides encoding these polypeptides are also encompassed by the invention.

 This gene is expressed in activated neutrophils.

10 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and other immune or hematopoietic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
15 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal
20 fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

 The tissue distribution in neutrophils indicates that the protein products of this gene are useful for the study and treatment of immune disorders. Moreover, this gene
25 product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including
30 arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated

cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 561 of SEQ ID NO:91, b is an integer of 15 to 575, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 82

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

LLRSALXSPHLPTPVPLV (SEQ ID NO:791),

QXRNLAQEAFKWIPQDRPTVRSRMRGLSIRLPILASNCCALPFXXTSPLQC

LWSCHCSFQANTGLAS (SEQ ID NO:792),

QMTQEPPTSVRAHGIAAWGNGCRDKNTKRLIQYWPESCSGMTKGTGVGRW

GEXRAERSS (SEQ ID NO:793), and/or HGIAAWGNGCRDKNTKRLIQY (SEQ ID NO:794). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,

96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

- 5 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in neutrophils.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
- 10 inflammatory and other immune or hematopoietic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain
- 15 tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 20 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 330 as residues: Ala-83 to Thr-91.

- The tissue distribution in neutrophils indicates that the protein products of this gene are useful for the study and treatment of immune disorders. Moreover, the expression of this gene product in neutrophils indicates a role in the regulation of the
- 25 proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene
- 30 product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease,

inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue
 5 injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may
 10 show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of
 15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 625 of SEQ ID NO:92, b is an
 20 integer of 15 to 639, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 83

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In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: CERSGYTRMAMDT (SEQ ID NO:795),
 TGSILAVGKKYSLGSYSRGDWHMRVVGLRGLGASTLQGLLIGIKPNKPQGRG
 30 KLQGRSSRKDTVLWPSPEHPHVMVMAILVYPDLSHYSNPHSTPAALLGCWPP
 FREGEILGLQRPQGWPEERC DRPWLP PC (SEQ ID NO:796),
 GSYSRGDWHMRVVGLRGLGASTLQGLLIG (SEQ ID NO:797), and/or

STPAALLGCWPPFREGEILGLQRPGQW (SEQ ID NO:798). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in human neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and inflammatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein products of this gene are useful for diagnosis and treatment of disorders of the inflammatory and immune systems. Moreover, expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be

also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 844 of SEQ ID NO:93, b is an integer of 15 to 858, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 84

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

30 TMGTWVDWLTTNTAHTPAIAAAICAEDFPQRHCGSVERSPDQAC (SEQ ID NO:799), and/or TNTAHTPAIAAAICAEDFPQRHC (SEQ ID NO:800). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as

described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in human neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory and immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the inflammatory and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein products of this gene are useful for diagnosis and treatment of disorders of the immune and inflammatory systems. Moreover, the expression of this gene product indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis,

granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:94, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 85

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In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: MSPETKGKGSRFPLK (SEQ ID NO:801),
CQNKCSSETTCGRTRRESNKQARAMAFIFKGKDLFPFVSGDIQPKSSGSMAPD
QQGLCYLGSWRSHLYCRLLPMDQVSPALC (SEQ ID NO:802),
KPSPGLAYCSLSWSFHMLFLNICSGITIPVILSSGPSHLSTLSLAVSPRRPGTWV
KACSCWCP (SEQ ID NO:803), NKQARAMAFIFKGKDLFPFVSGDI (SEQ ID

30

NO:804), YLGSWRSHLYCRLLPMDQVSP (SEQ ID NO:805), and/or GITIPVILSSGPSHLSTLSLAVSPR (SEQ ID NO:806). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 This gene is expressed in activated neutrophils.

 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and immune or hematopoietic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and inflammatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in neutrophils indicates that the protein products of this gene are useful for diagnosis and treatment of diseases of the inflammatory and immune systems. Moreover, the expression of this gene product indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin,

the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 412 of SEQ ID NO:95, b is an integer of 15 to 426, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 86

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: LERLGVGRGLE (SEQ ID NO:807),
DLPPCWTTLKEHQCFMQYQLFTIQCKVVEQTICEDERKMESTCLTLXPESV

RQXCPATLWSSMNIC (SEQ ID NO:808), and/or
TNRVXLSWRKEEQRMGRGTETGAKDKGRDFLERGSRGWQLYTGAADTEEV
(SEQ ID NO:809) . Moreover, fragments and variants of these polypeptides (such as,
for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
5 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
encoded by the polynucleotide which hybridizes, under stringent conditions, to the
polynucleotide encoding these polypeptides) are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
invention. Polynucleotides encoding these polypeptides are also encompassed by the
10 invention.

This gene is expressed in activated neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
15 inflammation and immune system disorders. Similarly, polypeptides and antibodies
directed to these polypeptides are useful in providing immunological probes for
differential identification of the tissue(s) or cell type(s). For a number of disorders of
the above tissues or cells, particularly of the inflammatory and immune system,
expression of this gene at significantly higher or lower levels may be routinely
20 detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous
and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial
fluid and spinal fluid) or another tissue or cell sample taken from an individual having
such a disorder, relative to the standard gene expression level, i.e., the expression
level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 334 as residues: Met-1 to Gly-6, Gly-32 to Pro-43, Leu-55 to Gln-60.

The tissue distribution in neutrophils indicates that the protein products of this
gene are useful for diagnosis and treatment of disorders of the immune and
inflammatory system. Moreover, the expression of this gene product indicates a role
30 in the regulation of the proliferation; survival; differentiation; and/or activation of
hematopoietic cell lineages, including blood stem cells. This gene product may be
involved in the regulation of cytokine production, antigen presentation, or other

processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 830 of SEQ ID NO:96, b is an integer of 15 to 844, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 87

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

EQVLALLWPRFELILEMNVQSVRSTDPQRLGGLDTRPHYTTTRYAEFSSALVSI
 NQTIPNERTMQLLGQLQVEVENFVLRVAAEFSSRKEQLVFLINNYDMMLGVL
 MERAADDSKEVESFQQLNARTQEFIEELLSPFPGGLVAFVKEAEALIERGQA
 ERLRGEEARVTQLIRGFGSSWKSSVESLSQDVMRSFTNFRNGTSIIQG (SEQ ID
 5 NO:810), ALLKYRFFYQFLGNERATAKEIRDEYVETLSKIYLSYRSYL
 GRMLKVQYEEVAEKDDLGMVEDTAKKGFXSKPSLRSRNTIFTLGTRGSVISP
 TELEAPILVPHTAQR (SEQ ID NO:811),
 EQRYPFALFRSQHYXLLDNSCREYLFICEFFVVS GPXAHDLFHAVMGRTLS
 MTLKHLD SYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPALDRYW (SEQ ID
 10 NO:812), GGLDTRPHYTTTRYAEFSSALVSINQ (SEQ ID NO:813),
 SRKEQLVFLINNYDMMLGVL (SEQ ID NO:814),
 ALLKYRFFYQFLGNERATAKEIRDEYVETLSKIYLSYRSYLGRMLKVQYE
 EVAEKDDLGMVEDTAKKGFXSKPSLRSRNTIFTLGTRGSVISPTELEAPILVPH
 TAQRXEQRYPFALFRSQHYXLLDNSCREYLFICEFFVVS GPXAHDLFHAVM
 15 GRTLSMTLKHLD SYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPALDRYWEQ
 VLALLWPRFELILEMNVQSVRSTDPQRLGGLDTRPHYTTTRYAEFSSALVSIN
 QTIPNERTMQLLGQLQVEVENFVLRVAAEFSSRKEQLVFLINNYDMMLGVL
 MERAADDSKEVESFQQLNARTQEFIEELLSPFPGGLVAFVKEAEALIERGQA
 ERLRGEEARVTQLIRGFGSSWKSSVESLSQDVMRSFTNFRNGTS (SEQ ID
 20 NO:815),
 PADLRAVSGTSEVGLMLLELHHKVVNDELSPGREGSELRLGQHPVEAMIEL
 DQLGQRSLNDTGAISEVGETPHYILTQRFH (SEQ ID NO:816), and/or
 GPHPGASHSAAXEQRYPFALFRSQHYXLLDNSCREYLFICEFFVVS GPXAHDL
 LFHAVMGRTLSMTLKHLD SYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPAL
 25 DRYWGTGACLAMATV (SEQ ID NO:817). Moreover, fragments and variants of
 these polypeptides (such as, for example, fragments as described herein, polypeptides
 at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these
 polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under
 stringent conditions, to the polynucleotide encoding these polypeptides) are
 30 encompassed by the invention. Antibodies that bind polypeptides of the invention are
 also encompassed by the invention. Polynucleotides encoding these polypeptides are
 also encompassed by the invention.

The translation product of this gene shares sequence homology with a suppressor of actin mutation which is thought to be important in mutation suppression.

This gene is expressed primarily in fetal liver.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic or metabolic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver or cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another
15 tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 335 as residues: Val-53 to Arg-60, Thr-88 to Thr-94, Ala-142 to Ser-150, Gly-
20 188 to Glu-196, Gly-208 to Ser-214, Thr-227 to Gly-232, Lys-279 to Phe-285.

The tissue distribution in liver, combined with the homology to a highly conserved suppressor of actin mutation, suggest that the protein product of this gene is useful for diagnosis and treatment of liver disorders or cancer. Similarly, the protein product of this gene is useful for the detection and treatment of
25 hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed
30 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1971 of SEQ ID NO:97, b is an integer of 15 to 1985, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 88

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

YEGKEFDYVFSIDVNEGGPSYKLPYNTSDDPWLTAYNFLQKNDLNPMFLDQ
 VAKFIIDNTKGQMLGLGNPSFSDPFTGGGRYVPGSSGSSNTLPTADPFTGAGR
 YVPGSASMGTTMAGVDPFTGNSAYRSAASKTMNIYFPKKEAVTFDQANPTQI
 LGKLELNGTAPEEKKLTEDDLILLEKILSLICNSSSEKPTVQQLQILWKAINCP
 EDIVFPALDILRLSIKHPSVNENFCNEKEGAQFSSHLINLLNPKGKPANQLLAL
 RTFCNCFVGQAGQKLMMSQRESLM SHAIELKSGSNKNI (SEQ ID NO:818),
 HIALATL ALNYSVCFHKD (SEQ ID NO:819),
 HNIEGKAQCLSLISTILEVVQDLEATFRLLVALGTLISDDSNVQLAKS (SEQ
 ID NO:820), LGVDSQIKKYSSVSEPAKVSECCRFILNLL (SEQ ID NO:821),
 YEGKEFDYVFSIDVNEGGPSYKLPYNTSDDPWLTAYNFLQKNDLNPMFLDQ
 VAKFIIDNTKGQMLGLGNPSFSDPFTGGGRYVPGSSGSSNTLPTADPFTGAGR
 YVPGSASMGTTMAGVDPFTGNSAYRSAASKTMNIYFPKKEAVTFDQANPTQI
 LGKLELNGTAPEEKKLTEDDLILLEKILSLICNSSSEKPTVQQLQILWKAINCP
 EDIVFPALDILRLSIKHPSVNENFCNEKEGAQFSSHLINLLNPKGKPANQLLAL
 RTFCNCFVGQAGQKLMMSQRESLM SHAIELKSGSNKNIHIALATLALNYSVC
 FHKDHNIEGKAQCLSLISTILEVVQDLEATFRLLVALGTLISDDSNVQLAKSL

GVDSQIKKYSSVSEPAKVSECCRFLNLL (SEQ ID NO:822),
 LNLLITQKVKCWDLGIPAFQIHLQVVVG (SEQ ID NO:823),
 IKHPSVNENFCNEKEGAQFSSHLLNLLNP (SEQ ID NO:824),
 AIELKSGSNKNIHIALATLALN (SEQ ID NO:825),
 5 VQLAKSLGVDSQIKKYSSVSEPA (SEQ ID NO:826),
 YEGKEFDYVFSIDVNEGGPSYKLPYN (SEQ ID NO:827),
 AYNFLQKNLNPMLDQVAKFIIDNT (SEQ ID NO:828),
 SFSDPFTGGGRYVPG (SEQ ID NO:829), TADPFTGAGRY (SEQ ID NO:830),
 TTMAGVDPFTGNSAYRSAA (SEQ ID NO:831), NIYFPKKEA (SEQ ID NO:832),
 10 TFDQANPTQILGKLKELNG (SEQ ID NO:833),
 PEDIVFPALDILRLSIKHPSVNENFCNEKE (SEQ ID NO:834),
 QFSSHLLNLLNPKG KPANQLLALRTFCNCFV (SEQ ID NO:835), and/or
 QAGQKLMMMSQRESLMSHAIELKSGSN (SEQ ID NO:836). Moreover, fragments
 and variants of these polypeptides (such as, for example, fragments as described
 15 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%
 identical to these polypeptides and polypeptides encoded by the polynucleotide which
 hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 20 these polypeptides are also encompassed by the invention.

These polypeptides share significant homology with phospholipase A2
 activating protein, which is thought to be important in signal transduction (see, e.g.,
 Wang et al., Gene 161(2):237-241 (1995)). The gene encoding the disclosed cDNA is
 believed to reside on chromosome 9. Accordingly, polynucleotides related to this
 25 invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in endothelial cells, to a less extent in
 placenta, endometrial stromal cells, osteosarcoma, testis tumor, muscle, and infant
 brain that are likely to be rich in blood vessels.

Polynucleotides and polypeptides of the invention are useful as reagents for
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 disorders of the vascular system, aberrant angiogenesis, tumor angiogenesis, or

related disorders of endothelial tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system or tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial, placenta, skeletal, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in endothelial cells and several potential highly vascularized tissues, combined with the homology to the highly conserved phospholipase A2 activating protein suggest that this gene may be involved in transducing signals for endothelial cells in angiogenesis or vasculogenesis. Furthermore, the protein may show utility for the treatment, and/or prevention of embolism, thrombosis, aneurysm, atherosclerosis, microvascular disease, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1402 of SEQ ID NO:98, b is an integer of 15 to 1416, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 89

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- YPNQDGDILRDQVLHEHIQRLSKVVTANHRALQIPEVYLREAPWPSAQSEIRT
 5 ISAYKTPRDKVQCILRMCSTIMNLLSLANEDSVPGADDFVPVLVFLIKANPP
 CLLSTVQYISSFYASCLSGEESYWWMQFTA AVE (SEQ ID NO:837),
 YPNQDGDILRDQVLHEHIQRLSKVVTANHRALQIPEVYLREAPWPSAQSEIRT
 ISAYKTPRDKVQCILRMCSTIMNLLSLANEDSVPGADDFVPVLVFLIKANPP
 CLLSTVQYISSFYASCLSGEESYWWMQFTA AVEFIKTI (SEQ ID NO:838),
 10 YPNQDGDILRDQVL (SEQ ID NO:839), EAPWPSAQSEI (SEQ ID NO:840),
 PVLVFLIKANP (SEQ ID NO:845), SGEESYWWMQFTA AVEFIKTI (SEQ ID
 NO:841), ADDFVPVLVFLIK ANPP (SEQ ID NO:842), YKTPRDKVQCIL (SEQ
 ID NO:843), and/or GADDFVPV LVFLIK (SEQ ID NO:844). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 15 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 20 these polypeptides are also encompassed by the invention.

- The translation product of this gene shares sequence homology with human
 Ras inhibitor and yeast VPS9p which is thought to be important in Golgi vacuole
 transport. The gene encoding the disclosed cDNA is believed to reside on
 chromosome 9. Accordingly, polynucleotides related to this invention are useful as a
 25 marker in linkage analysis for chromosome 9.

This gene is expressed primarily in T cells and melanocytes.

- Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 30 immune, hematopoietic, or integumentary disorders, such as dysfunctions and
 disorders involving T cells and melanocytes. Similarly, polypeptides and antibodies
 directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells and melanocytes, combined with the homology to a Ras inhibitor, indicates that the protein product of this gene is useful for regulating signal transduction; the diagnosis and treatment of disorders involving T cells and melanocytes, and potentially in the prevention or study of immune responses to aberrant integumentary cells and tissues, particularly in tumors and cancers, such as skin cancers. Moreover, the protein product of this gene is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, Athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal

chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1746 of SEQ ID NO:99, b is an integer of 15 to 1760, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 90

The translation product of this gene shares sequence homology with neuronal olfactomedin-related ER localized protein which is thought to be important in the maintenance, growth, or differentiation of chemosensory cilia on the apical dendrites of olfactory neurons. Moreover, the protein also shares homology with the conserved human AMY protein which is thought to be a glial cell-specific transforming protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

25 SARASTQPPAGQHGPC (SEQ ID NO:846),
 MPGRWRWQRDMHPARKLLSLLFLILMGTELTQD (SEQ ID NO:847),
 SAAPDSLLRSSKGSTRGSL (SEQ ID NO:848), AAIVWRGKSESRIAKTPGI
 (SEQ ID NO:849), FRGGGTLVLPPTHTPEWLIL (SEQ ID NO:852),
 PLGITLPLGAPETGGGD (SEQ ID NO:850), NSARAS
 30 TQPPAGQHGPCMPGRWRWQRD (SEQ ID NO:853),
 YIVQGTTSPFEMPTIPTPARHRAPHSPAGHVATAPQALHIKPAMHTAGRHAG
 CPSRSQ RHNPHRLFLEPPRAALCPKGG (SEQ ID NO:854),

ASNAHSWPARWLPFQVSAAQSPPPVSGAPKGSVMPKGRMSHSGVCVGGRTK
VPPPLKMPGVLAIRLSLFPLQMTIAAKDPLVLPFELLSRESGAAES (SEQ ID
NO:855), GRMSHSGVCVGGRTKVPPPLKMPGVLA (SEQ ID NO:856), and/or
CAAETWKGSQRAGQLCALLA (SEQ ID NO:851). Moreover, fragments and
5 variants of these polypeptides (such as, for example, fragments as described herein,
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,
under stringent conditions, to the polynucleotide encoding these polypeptides) are
encompassed by the invention. Antibodies that bind polypeptides of the invention are
10 also encompassed by the invention. Polynucleotides encoding these polypeptides are
also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
9. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 9.

15 This gene is expressed in pineal gland.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
neurological and endocrine disorders. Similarly, polypeptides and antibodies directed
20 to these polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the neurological or endocrine systems, expression of
this gene at significantly higher or lower levels may be routinely detected in certain
tissues or cell types (e.g., neural, endocrine, and cancerous and wounded tissues) or
25 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or
another tissue or cell sample taken from an individual having such a disorder, relative
to the standard gene expression level, i.e., the expression level in healthy tissue or
bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
30 NO: 338 as residues: Leu-20 to Ala-26, Arg-32 to Arg-39, Thr-104 to Gly-112.

The tissue distribution in pineal gland, combined with the homology to both
the olfactomedin-related, and AMY proteins, indicates that the protein product of this

gene is useful for maintenance, growth, or differentiation of neuron cells in pineal gland. Therefore, the protein product of this gene may be useful for the diagnosis and treatment of neurological disorders in pineal gland. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 585 of SEQ ID NO:100, b is an integer of 15 to 599, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 91

This gene is expressed primarily in prostate and apoptotic T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, immune, or hematopoietic disorders, particularly prostate disease and T cell dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate and T-cells indicates that the protein product of this gene is useful for the detection of abnormal activity in prostate and T cells, such as proliferative conditions of the prostate, or possibly treatment of this abnormality. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial

utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 770 of SEQ ID NO:101, b is an integer of 15 to 784, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 92

The gene encoding the disclosed cDNA is believed to reside on chromosome
20 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in prostate, and to a lesser extent, in smooth muscle cells, fibroblasts, and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for
25 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in prostate or vascular tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
30 the above tissues or cells, particularly of the prostate or vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, musculoskeletal, cancerous and wounded tissues)

or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 340 as residues: Ser-38 to Lys-46.

The tissue distribution in prostate and smooth muscle indicates that the protein product of this gene is useful for regulating the function of prostate or highly vascularized tissues, such as the placenta. Similarly, the protein product of this gene
10 may be useful in the treatment and/or detection of vascular disorders which include, but are not limited to, stroke, embolism, thrombosis, aneurysm, microvascular disease, or atherosclerosis. The protein may also show utility in the treatment or detection of proliferative disorders of the prostate or male reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tumor
15 marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 390 of SEQ ID NO:102, b is an integer of 15 to 404, where both a and b correspond to the positions of nucleotide
25 residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 93

- 30 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GHQTAPETPSRSD (SEQ ID NO:857). Moreover, fragments and variants of this polypeptide (such as, for

example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind
5 polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in embryos and fetal tissues, and to a lesser extent, in proliferative tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in embryonic development and cell proliferation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
15 disorders of the above tissues or cells, particularly of the embryonic tissues and proliferative cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, differentiating, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue
20 or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in embryonic and fetal tissues indicates that the protein product of this gene is useful for the diagnosis or treatment of abnormalities in
25 developing and proliferative cells and organs. Similarly, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation
30 and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2204 of SEQ ID NO:103, b is an integer of 15 to 2218, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

The translation product of this gene shares sequence homology with a transformation related protein which is thought to be important in transformation.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: SQTDR (SEQ ID NO:858). Polynucleotides encoding this polypeptides are also encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in female reproductive tissues, i.e., breast cancer cells, placenta, and ovary, and to a lesser extent, in fetal lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer or dysfunction of reproductive tissues, in addition to pulmonary or

developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproduction system, expression of this gene at

5 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, reproductive, ovarian, breast, placental, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, pulmonary surfactant or sputum, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative

10 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 342 as residues: Ser-50 to Pro-61.

The tissue distribution in female reproductive tissues, combined with the

15 homology to the transformation related protein, indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions caused by transformation, i.e. tumorigenesis in reproductive organs, (e.g. breast, placenta, and ovary). Similarly, expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of

20 cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein may also be useful in the treatment or detection of a

25 variety of pulmonary conditions, including, but not limited to emphysema, ARDS, cystic fibrosis, asthma, etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1337 of SEQ ID NO:104, b is an integer of 15 to 1351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 95

10

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

NIYFKEKRKRGGAKMAGAIEN (SEQ ID NO:859),

VYLCAYTSTINVTVTANAKLINMCCLVDSNTRSCVVIDEGIFRSAEQFLIKFR

15 NKQSTIFPRFTWELHSIGLVFSIVFMGWCIEHQSKDIQIPHPIDACEKGTVHL

DCDAAPFPMAFRYLTNDEEDDSHGSAGQGDKHEELEPKN (SEQ ID NO:860),

KMPCRMSPNSSIQVQSNPMENHSTGILIKVMEIPRAKMTFSRSTGGRDIMVILL

QYHTIMMKMLGVRKVFMANHTLVKPPFWWIPTNRISFISPIPTLIFFSFTGSR

MFKR (SEQ ID NO:861),

20 TTKSEKMQKSPWTFPWLTVMTHLLSGLKWPMKEYHGNSSNAPSHLPRLQSM

RAVTMNVMSFLSWKLGLWPISFTF (SEQ ID NO:862),

IKFRNKQSTIFPRFTWELHSIGLVFSIVFMG (SEQ ID NO:863),

SSIQVQSNPMENHSTGILIKVMEIPRAKM (SEQ ID NO:864), and/or

LGVRKVFMANHTLVKPPFWWIPTNRISFISPIP (SEQ ID NO:865). Moreover,

25 fragments and variants of these polypeptides (such as, for example, fragments as described herein; polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
30 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

5 This gene is expressed primarily in testes, rhabdomyosarcoma, infant brain and to a lesser extent in some tumors and highly vascularized tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, 10 tumorigenesis, abnormal angiogenesis, reproductive, vascular, and/or neurological disorders. , Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor tissues or vascular tissues, expression of this gene at 15 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., muscle, neural, developmental, vascular, reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene 20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 343 as residues: Arg-46 to Trp-54, Pro-60 to Ile-69, Asn-116 to Ala-122, Arg- 147 to Lys-153, Ser-158 to Glu-170, Ile-399 to Ser-405, Pro-486 to Met-499, Pro-502 25 to Asp-508.

The tissue distribution in infant brain indicates that the protein product of this gene is useful for a range of disease states including treatment of tumor or vascular disorders and the treatment of neurological disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, 30 obsessive compulsive disorder and panic disorder. Moreover, expression within vascular tissues indicates that the protein product of this gene is useful in the treatment and/or detection of a variety of vascular conditions, which include but are

not limited to emphysema, atherosclerosis, thrombosis, microvascular disease, stroke or aneurysm. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
 5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
 10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2052 of SEQ ID NO:105, b is an integer of 15 to 2066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 96

The translation product of this gene is homologous to the *Clostridium perfringens* enterotoxin (CPE) receptor gene product and shares sequence homology
 20 with a human ORF specific to prostate and a glycoprotein specific to oligodendrocytes, both of which are tissue specific proteins. See e.g., Katahira et al. J Cell Biol. 136(6):1239-1247 (1997). PMID: 9087440; UI: 97242441.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: TMASMGLQV (SEQ
 25 ID NO:866),
 KSWMMLWAVQDTGTITIRPANRNTTPATIMVLALALSSSRQLVHLPPTTDSST
 PRAATMMLMMTRARAACRSCGSASSESYTLHCIWVPLCTTQFIHRPSQMVCE
 VTMLLPKAVTRHMGSAQHSMTASQPRTASAMPITCSPMEAIVQRPRELRT
 WKAEGIRLWGP (SEQ ID NO:867),
 30 LQVMGIALAVLGWLAVMLCCALPMWRVT (SEQ ID NO:868),
 SNIVTSQTIWEGLWMNCVVQST (SEQ ID NO:869),
 QMQCKVYDSLALPQDLQ (SEQ ID NO:870),

KCTNCLEDESAKAKTMIV(SEQ ID NO:871),
GVVFLLAGLMVIVPVSWSAHNIQDFYNPLVA (SEQ ID NO:872), and/or
CCNCPRTDKPY (SEQ ID NO:873). Moreover, fragments and variants of these
polypeptides (such as, for example, fragments as described herein, polypeptides at
5 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
and polypeptides encoded by the polynucleotide which hybridizes, under stringent
conditions, to the polynucleotide encoding these polypeptides) are encompassed by
the invention. Antibodies that bind polypeptides of the invention are also
encompassed by the invention. Polynucleotides encoding these polypeptides are also
10 encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
7. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 7.

This gene is expressed primarily in pancreas tumor and ulcerative colitis, and
15 to a lesser extent in several tumors and normal tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
metabolic, gastrointestinal, or proliferative disorders, such as pancreatic disorders,
20 ulcerative colitis, tumors and food poisoning. Similarly, polypeptides and antibodies
directed to these polypeptides are useful in providing immunological probes for
differential identification of the tissue(s) or cell type(s). For a number of disorders of
the above tissues or cells, particularly of the digestive system or tumorigenic system,
expression of this gene at significantly higher or lower levels may be routinely
25 detected in certain tissues or cell types (e.g., metabolic, gastrointestinal, pancreatic,
and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum,
plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
from an individual having such a disorder, relative to the standard gene expression
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
30 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 344 as residues: Gly-147 to Met-152, Cys-177 to Lys-188.

The tissue distribution in pancreas, combined with the homology to a prostate and oligodendrocyte-specific protein, indicates that the protein product of this gene is useful as a marker for the diagnosis or treatment of disorders in pancreas, ulcerative colitis, and tumors. Furthermore, identity to the human receptor for *Clostridium* 5 *perfringens* enterotoxin indicates that the soluble portion of this receptor could be used in the treatment of food poisoning associated with *Clostridia perfringens* by blocking the activity of the *perfringens* enterotoxin. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

10 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is 15 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1691 of SEQ ID NO:106, b is an integer of 15 to 1705, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 97

25 The translation product of this gene shares sequence homology with an ATPase from *Saccharomyces cerevisiae* which is thought to be important in metabolism (See Genbank Accession No.g1181253).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: PFTAIAGSEIFSLE 30 (SEQ ID NO:874), SKTEALTQAFR (SEQ ID NO:875), VVHTVSLHEIDVINSRTQGFLALF (SEQ ID NO:876), PGVLFIDEVHMLDIE (SEQ ID NO:877),

- AGIRQRFSARLWQLVSI MATVTATTKVPEIRDVTRIERIGAHSHIRGLGLDDAL
EPRQASQGMVVGQLAARRAAGVVLEMIREGKIAGRAVLIAGQPGTGKTAIAM
GMAQALGPDTPFTAIAGSEIFSLEMSKTEALTQAFRRSIGVRIKEETEIEGEVV
EIQIDRPATGTGSKVGKLT LKTTEMETIYDLGTKMIXSLTKDKVQAGDVITID
5 KATGKISKLG RSFTRARELRRYGLPDQVRAVPRWGAPETQGGGAHRVPARD
RRHQLSHPGLPGALLR (SEQ ID NO:878),
SPSTRRRARSPSWAAPSHAPANYDAMGSQTKFVQCPDGELQKRKEVVHTVS
LHEIDVINSRTQGFLALFSGDTGEIKSEVREQINAKVAEWREEGKAEIIPGVLF
DEVHMLDIESFSFLNRALES DMAPVQQVYGDAVRALVAGAPDSRDATVGGL
10 VPNSCSPGDPLVLERPPPRWXS (SEQ ID NO:879),
WIPRAAGIRHEATNRGITRIRGTSYQSPHGIPIDLLDRRHVTLQGPVEEGEALD
VQHVDLVDEQHSRDDRLALLAPLSHLGIDLLTDF (SEQ ID NO:880),
YDAMGSQTKFVQCPDGELQKRKEVVHTVSL (SEQ ID NO:881),
KAEIIPGVLFIDEVHMLDIESFSFLNRALES (SEQ ID NO:882), and/or
15 EATNRGITRIRGTSYQSPHGIPIDLLDR (SEQ ID NO:883). Moreover, fragments
and variants of these polypeptides (such as, for example, fragments as described
herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%
identical to these polypeptides and polypeptides encoded by the polynucleotide which
hybridizes, under stringent conditions, to the polynucleotide encoding these
20 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes and several hematopoietic cells.

- Polynucleotides and polypeptides of the invention are useful as reagents for
25 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
reproductive, immune, or hematopoietic disorders, particularly male infertility and
leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are
useful in providing immunological probes for differential identification of the
30 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
particularly of the hematopoietic system, expression of this gene at significantly
higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,

reproductive, immune, hematopoietic, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in
5 healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes and hematopoietic cells, combined with the homology to ATPases, indicates that the protein product of this gene is useful as a marker for the diagnosis and treatment of leukemia and other hematopoietic disorders. The protein may also show utility as a contraceptive, or for the treatment and/or
10 detection of aberrant testicular function. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or
15 induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds); stimulation of follicle stimulating hormone (for
20 control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of
25 the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
30 related to SEQ ID NO:107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1153 of SEQ ID NO:107, b is an integer of 15 to 1167, where both a and b correspond to the positions of nucleotide
 5 residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 98

10 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
 MRSARPSLGCLPSWAFSQALNI (SEQ ID NO:884),
 LLGLKGLAPAEISAVCEGNFN (SEQ ID NO:885),
 VAHGLAWSYYIGYLRLILPELQARIR (SEQ ID
 15 NO:886), TYNQHYNNLLRGAVSQRC (SEQ ID NO:887), ILLPLDCGVDPNLS
 MADPNIRFLDKLPQQTGDRAGIKDRVYSN (SEQ ID NO:888),
 SIYELLENGQRAGTCVLEYATPLQTLFAMSQYSQAGFSGEDRLEQ (SEQ ID
 NO:889),
 AKLFCRTLEDILADAPESQNNCRLLIAYQEPADDSSFSLSQEVLRLHLRQEEKEE
 20 VTVGSLKTSAPSTSTMSQEPellisgMEKPLPLRTDFS (SEQ ID NO:890),
 LRLHSEKLPLAARSAGPSLLVIIQSSQCPGRRYRGSYWRTVRACLGCPLRRG
 ALLLLSIYFYYSPLPNAVGPFTW (SEQ ID NO:892),
 VWLTPTFASWINCPSRPVTVLASRIGFTATASMSFWRTGSGRAPVSWSTPPPC
 RLCLPCHNTVKLALAGRIGLSRPNSSAGHLRTSWQMPLSLRTTAASLPTRNLQ
 25 MTAASRCPRRFSGTCGRRKRKRLWAA (SEQ ID NO:893),
 GVCQVSFMGPSRPTPHPSPLPLPGDAELSQWYQQAPSPSGSWSCSIIGEPQQK
 NGEEEAEFGVLNPPAPTLLQHQCGLSCRATLA (SEQ ID NO:894), and/or
 LLGLKGLAPAEISAVCEKGNFNVAHGLAWSYYIGYLRLILPEL (SEQ ID
 NO:891). Moreover, fragments and variants of these polypeptides (such as, for
 30 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,
 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in prostate BPH, and to a lesser extent, in bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, hematopoietic, or immune disorders, particularly benign prostatic hypertrophy, prostate cancer, or leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male urinary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, hematopoietic, immune, prostatic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 346 as residues: Ile-60 to Asn-69, Leu-106 to Asp-112, Glu-130 to Gly-136, Phe-160 to Glu-167, Pro-184 to Cys-190, Glu-197 to Ser-202, Arg-215 to Glu-221, Thr-237 to Pro-242.

25 The tissue distribution in prostate tissue indicates that the protein product of this gene is useful for the diagnosis or treatment of reproductive disorders, such as benign prostatic hypertrophy or prostate cancer. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may

also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:108 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1893 of SEQ ID NO:108, b is an integer of 15 to 1907, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 99

The gene encoding the disclosed cDNA is believed to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

25 This gene is expressed primarily in salivary gland.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders, particularly of the salivary gland. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of glandular tissues, expression of

this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. salivary gland, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, chyme, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
5 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in salivary glands indicates that the protein product of this gene is useful for the treatment and/or detection of disorders of or injuries to the salivary gland or other glandular tissue. Protein, as well as, antibodies directed
10 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:109 and may have been publicly available prior to conception
15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 597 of SEQ ID NO:109, b is an
20 integer of 15 to 611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 100

25

The translation product of this gene shares sequence homology with a *C.elegans* gene. Based upon its degree of conservation, an important cellular function can be attributed to this protein. When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating
30 sequence) promoter element. Thus, it is likely that this gene activates T-cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-

STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

DPRVRLNSLTCKHIFISLTQ (SEQ ID NO:902),

TMKLLKLRRNIVKLSLYRHFTN (SEQ ID NO:895),

TLILAVAASIVFIIWTTMKFRI (SEQ ID NO:896),

10 VTCQSDWRELWVDDAIWRLLFMILFVI (SEQ ID NO:897),

MVLWRPSANNQRFAFSPLSEEEEEDEQ (SEQ ID NO:898),

MVLWRPSANNQRFAFSPLSEEEEEDEQ (SEQ ID NO:899),

KEPMLKESFEGMKMRSTKQEPNGNSKVNKAQEDDL (SEQ ID NO:900),

NAFGRHSTAVK (SEQ ID NO:903),

15 ESCLLCGISEYPIQRXICPGCFDPCRFAFSSETLTGSNPGHHSQSGIWHRQATP
GVTLHKV VVAXALYLLFSGMEGVLRVTGAQTDLASLAFIPLAFLDTALCWW
IFISLTQTMKLLKLRRNIVKLSLYRHFTNTLILAVAASIVFIIWTTMKFRIVTCQ
SDWRELWVDDAIWRLLFMILFVIMVLWRPSANNQRFAFSPLSEEEEEDEQK
EPMLKESFEGMKMRSTKQEPNGNSKVNKAQEDDLKWVEENVPSVTDVALP

20 ALLDSDEERMITHFERSKME (SEQ ID NO:904), and/or

KWVEENVPSVTDVALPALDSDEERMITHFERSKME (SEQ ID NO:901).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the

25 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
30 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

This gene is expressed primarily in thyroid, and to a lesser extent, in osteoclastoma, kidney medulla, and lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine disorders, particularly thyroid dysfunction or cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, skeletal, urogenital, renal, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, pulmonary surfactant or sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 348 as residues: Lys-107 to Leu-124, Glu-150 to Thr-159, Pro-173 to Asp-179, Ser-192 to Ser-201.

The tissue distribution in thyroid, combined with the detected GAS biological activity, indicates that the protein product of this gene is useful for the diagnosis and treatment of thyroid dysfunction or cancer. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:110 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2618 of SEQ ID NO:110, b is an

integer of 15 to 2632, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 101

The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

10 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: YEPMDFXMALIYD (SEQ ID NO:905), IRHELTVLRDT RPACA (SEQ ID NO:906), and/or MDFXMALYD (SEQ ID NO:907). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,
15 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are
20 also encompassed by the invention.

This gene is expressed primarily in kidney cortex, and to a lesser extent, in adult brain, corpus colosum, hippocampus, and frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
25 and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, kidney disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and renal system,
30 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adult brain, corpus colosum, hippocampus, and
5 frontal cortex indicates that the protein product of this gene is useful for treatment or diagnosis of neurological disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep
10 patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, The tissue distribution in kidney indicates that this gene or gene product could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal
15 tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker
20 and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:111 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2235 of SEQ ID NO:111, b is an integer of 15 to 2249, where both a and b correspond to the positions of nucleotide
30 residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 102

The translation product of this gene shares sequence homology with F15C11.2 of *C. elegans* which is of unknown function.

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- MQEMMRNQDRALSNLESIPGGYNA (SEQ ID NO:908),
 LRRMYTDIQEPMLSAAQEQFGGNPF (SEQ ID NO:909),
 ASLVSNTSSGEGSQPSRTENRDPLPNPWAPQT (SEQ ID NO:910),
 10 SQSSSASSGTASTVGGTTGTASGTSGQSTTAPNLVPGVGASMFNTPGMQSLL
 QQITENPQLMQNMLSAPY (SEQ ID NO:911),
 MRSMMQSLSQNPDLAAQMMLNNPLFAGNPQLQEQMRQQLPTFLQQ (SEQ
 ID NO:912),
 MQNPDTLSAMSNPRAMQALLQIQQGLQTLATEAPGLIPGFTPGLGALGSTGG
 15 SSGTNGSNATPSENTSPTAGT (SEQ ID NO:913),
 TEPGHQQFIQQMLQALAGVNPQLQNPEVRFQQQLEQLSAMGFLNREANLQA
 LIATGGDINAAIERLLGSQPS (SEQ ID NO:914),
 RNPAMMQEMMRNQDRALSNLESIPGGYNALRRMYTDIQEPMLSAA (SEQ ID
 NO:915), GNPFFASLVSNTSS (SEQ ID NO:916), ENRDPLPNPWA (SEQ ID
 20 NO:917), GKILKDQDTLSQHGIHD (SEQ ID NO:918), GLTVHLVIKTQNRP
 (SEQ ID NO:919), SELQSQMQRQLLSNPEMM (SEQ ID NO:920),
 PEISHMLNNPDIMR (SEQ ID NO:921), and/or RQLIMANPQMQLIQRNP (SEQ
 ID NO:922). Moreover, fragments and variants of these polypeptides (such as, for
 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,
 25 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 encoding these polypeptides) are encompassed by the invention. Antibodies that
 bind polypeptides of the invention are also encompassed by the invention.
 Polynucleotides encoding these polypeptides are also encompassed by the invention.

- 30 This gene is expressed primarily in breast.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of tumor systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. breast, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast indicates that the protein product of this gene is useful for treatment and diagnosis of some types of breast cancer. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:112 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2184 of SEQ ID NO:112, b is an integer of 15 to 2198, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 103

The translation product of this gene shares sequence homology with secreted serine proteases and lysozyme C precursor, which is thought to be important in bacteriolytic function.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

NLCHVDCQDLLNPNULLAGIHCAKRIVS (SEQ ID NO:923),

LDGFEGYSLSDWLCLAFVESKFN (SEQ ID NO:924),

5 NENADGSFDYGLFQINSHYWCN (SEQ ID NO:925),

NLCHVDCQDLLNPNULLAGIHCAKRIVS (SEQ ID NO:926), and/or

EPSALSCTSSPPR (SEQ ID NO:927). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides

10 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infection, immune system disorders, reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, cancerous and

20 wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 351 as residues: Ile-62 to Phe-70, Asn-78 to Asn-84.

The tissue distribution in testes, combined with the homology to lysozyme C precursor indicates that the protein product of this gene is useful for boosting the monocyte-macrophage system, and for enhancing the activity of immune agents. Alternatively, the tissue distribution indicates that the protein product of this gene is
5 useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is
10 believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone
15 formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:113 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1029 of SEQ ID NO:113, b is an integer of 15 to 1043, where both a and b correspond to the positions of nucleotide
25 residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 104

30 This gene is expressed primarily in apoptotic T-cell, and to a lesser extent in CD34(+) cells..

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these

5 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph,

10 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that the protein product of this gene

15 is useful for treatment and diagnosis of some immune disorders. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the

20 protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion

25 of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed

30 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:114 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
 5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 689 of SEQ ID NO:114, b is an integer of 15 to 703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 105

The translation product of this gene shares sequence homology with ARI protein of Drosophila (See Genbank Accession 2058299; EMBL: locus
 15 DMARIADNE, accession X98309), which is thought to be important in axonal path-finding in the central nervous system.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
 IREVNEVIQNPAT (SEQ ID NO:928),
 20 ITRILLSHFNWDKEKLMERYFDGNLEKLFA (SEQ ID NO:929),
 NTRSSAQDMPQCICYLNYPNSYF (SEQ ID NO:930), TGL
 ECGHKFCMQCWSEYLTTKIMBEGMGQTISCPAHG (SEQ ID NO:936),
 CDILVDDNTVMRLITDSKVKLKYQHLITNSFVECNRLWKWCPAPDCHHVVKV
 QYPDAKPV (SEQ ID NO:931),
 25 CDILVDDNTVMRLITDSKVKLKYQHLITNSFVECNRLWKWCPAPDCHHVVKV
 (SEQ ID NO:932),
 GCNHMVCRNQNCCKAEFCWVCLGPWEPHGSAWYNCNRYNEDDAKAARDA
 QERSRAALQRYL (SEQ ID NO:933),
 FYCNRYMNHMQSLRFEHKLYAQVKQKMEEMQQHNMSWIEVQFLKKAVDV
 30 LCQCRATLMYT (SEQ ID NO:934), and/or
 YVFAFYLLKNNQSIIFENNQADLENATEVLSGYLERDISQDSLQDIKQKVQDK
 YRYCESR (SEQ ID NO:935). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in adult brain, and to a lesser extent in testes, endometrial tumor, melanocytes, and infant brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases or injuries involving axonal path development. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, testes, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adult brain, combined with the homology to ARI protein indicates that the protein product of this gene is useful for the treatment of disease states or injuries involving axonal path development, including neurodegenerative diseases and nerve injury, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well

as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:115 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3670 of SEQ ID NO:115, b is an integer of 15 to 3684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 106**

The translation product of this gene shares sequence homology with cytochrome b561 [*Sus scrofa*] which is thought to be an integral membrane protein of neuroendocrine storage vesicles of neurotransmitters and peptide hormones. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in frontal cortex, and to a lesser extent in rhabdomyosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 354 as residues: Ser-18 to Pro-24.

The tissue distribution in frontal cortex, combined with the homology to cytochrome b561 [*Sus scrofa*] indicates that the protein product of this gene is useful for the treatment and diagnosis of neurological disorders. This gene may also be important in the regulation of some types of cancers. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the brain and nervous system. Elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:116 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1951 of SEQ ID NO:116, b is an integer of 15 to 1965, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 107

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MWGYLFVDAAWNFLGCLICGW (SEQ ID NO:937),

MHFISSGNVSAIRSSILLRXSLSYLGNCLRVSAIFVYFLLFLLLS (SEQ ID

5 NO:938), and/or

MDQALRGSPSEGFSTDPSPPQVGRQIPSFPPWRRLVLPKASGCFLEREWLVCV

FKLRTRPGAEAHAYNSSILGGRGKGIT (SEQ ID NO:939). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%

10 identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in pancreas tumor, and to a lesser extent in cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

20 pancreatic tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

25 types (e.g. pancreas, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 355 as residues: Pro-22 to Phe-33.

The tissue distribution in pancreas tumors indicates that the protein product of this gene is useful for diagnosis and treatment of pancreatic tumors, and/or tumors of metabolic tissues and cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the
5 above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:117 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 489 of SEQ ID NO:117, b is an integer of 15 to 503, where both a and b correspond to the positions of nucleotide
15 residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 108

20 The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

25 MLPALASCCHFSPPEQAARLKKLQEQEKQKVEFRKRMEKEVSDFIQDSGQI
KKKFQPMNKIERSILHDVVEVAGLTSFSFGEDDDCRYVMIFKKEFAPSDEELD
SYRRGEEWDPQKAEEKRNXXKELAQ RQ (SEQ ID NO:940),
EEEEAAQQGPVVVSPASDYKDKYSHLIGKGAAKDAAHMLQANKTYGCXPVA
NKR DTRSIEEAMNEIRAKKRLRQSGE (SEQ ID NO:941),
30 PPRRPAQLPLTPGAGQGAGRDKAAAIRAHPGAPPLNHL LP (SEQ ID NO:942),
AVPQAGGKQVFDLSPLELGYVRGMCVCV (SEQ ID NO:943) and/or
MLPALASCCHFSPPEQAARLKKLQEQEKQKVEFRKRMEKEVSDFIQDSGQI

KKKFQPMNKIERSILHDVVEVAGLTSFSFGEDDDCRYVMIFKKEFAPSDEELD
SYRRGEEWDPQKAEEKRNXXKELAQREQEEAAQQGPVVVSPASDYKDKYSHL
IGKGAAKDAAHMLQANKTYGCPVANKRDTRSIEEAMNEIRAKKRLRQSGE
(SEQ ID NO:944). Moreover, fragments and variants of these polypeptides (such as,
5 for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
encoded by the polynucleotide which hybridizes, under stringent conditions, to the
polynucleotide encoding these polypeptides) are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
10 invention. Polynucleotides encoding these polypeptides are also encompassed by the
invention.

The translation product of this gene shares sequence homology with FSA-1,
which may play a role as a structural protein component of the acrosome. The
mammalian spermatozoon undergoes continuous modifications during
15 spermatogenesis, maturation in the epididymis, and capacitation in the female
reproductive tract. Only the capacitated spermatozoa are capable of binding the zona-
intact egg and undergoing the acrosome reaction. The fertilization process is a net
result of multiple molecular events which enable ejaculated spermatozoa to recognize
and bind to the egg's extracellular coat, the zona pellucida (ZP). Sperm-egg
20 interaction is a species-specific event which is initiated by the recognition and binding
of complementary molecule(s) present on sperm plasma membrane (receptor) and the
surface of the ZP (ligand). This is a carbohydrate-mediated event which initiates a
signal transduction cascade resulting in the exocytosis of acrosomal contents. This
step is believed to be a prerequisite which enables the acrosome reacted spermatozoa
25 to penetrate the ZP and fertilize the egg. Recently, another group published this gene,
calling it sperm acrosomal protein [Homo sapiens] (Proc. Natl. Acad. Sci. U.S.A.
95 (14), 8175-8180 (1998)).

This gene is expressed primarily in fetal kidney and sperm.

Polynucleotides and polypeptides of the invention are useful as reagents for
30 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
male reproductive disorders, especially involving acrosomal dysfunction. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. sperm, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 356 as residues: Met-12 to Gln-30, Lys-35 to Val-46, Arg-49 to Val-56, Gln-61 to Glu-77, Gly-96 to Cys-101, Glu-110 to Lys-139, Leu-141 to Gln-151, Ser-161 to Tyr-167, Asn-196 to Ile-203, Arg-211 to Ser-227.

15 The tissue distribution in sperm, combined with the homology to FSA-1 and the Homo sapiens sperm acrosomal protein indicates that the protein product of this gene is useful for the treatment of infertility due to acrosomal dysfunction of sperm. Protein may also be useful as a contraceptive either alone, or in combination with other therapies. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:118 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1057 of SEQ ID NO:118, b is an integer of 15 to 1071, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 109

This gene is expressed primarily in pituitary tissue, and to a lesser extent in epididymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. epididymus, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 357 as residues: Met-1 to Trp-6.

Because the gene is found in both pituitary and epididymus, this indicates that the protein product of this gene is useful for the treatment and diagnosis of male reproductive disorders. This may involve a secreted peptide produced in the pituitary targeting the epididymus. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:119 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:119, b is an

integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.

5 **FEATURES OF PROTEIN ENCODED BY GENE NO: 110**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: LLCPVLSNGXSWNFPHPSPQEYSFHGFHSTRLWI (SEQ ID NO:945), and/or
10 PSTPWFLFLLGLTCPFSTSHPRWDSIPP (SEQ ID NO:946). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these
15 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in resting T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T-cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
25 particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that the protein product of this gene is useful for the treatment and diagnosis of certain immune disorders, especially those involving T-cells. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:120 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 268 of SEQ ID NO:120, b is an integer of 15 to 282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 111

The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

This gene is expressed primarily in cerebellum and whole brain, and to a lesser extent in infant brain and fetal kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 359 as residues: Asp-48 to Gly-55.

The tissue distribution in cerebellum and whole brain indicates that the protein product of this gene is useful for diagnosis and treatment of neurological disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:121 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2621 of SEQ ID NO:121, b is an integer of 15 to 2635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 112

The translation product of this gene shares sequence homology with yeast mitochondrial ribosomal protein, which is homologous to ribosomal protein s15 of
15 *E.coli*, which is thought to be important in the early assembly of ribosomes (See Genbank Accession No. M38016). The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in developmental tissues.

20

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, development of cancers and tumors in addition to healing wounds. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
25 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. developmental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,
30 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in developmental tissues, combined with the homology to ribosomal protein s15 of *E. coli* indicates that the protein product of this gene is
5 useful for the diagnosis and/or treatment of diseases related to the assembly of ribosomes in the mitochondria, which is important in the translation of RNA into protein. Therefore, this indicates that the protein product of this gene is also useful for the diagnosis and intervention of multiple tumors, as well as in healing wounds, which are thought to be under similar regulation as developmental tissues. Protein, as
10 well as, antibodies directed against the protein have utility as tumor markers, in addition to immunotherapy targets, for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:122 and may have been publicly available prior to conception
15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 980 of SEQ ID NO:122, b is an
20 integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 113

25

For purposes of this application, this gene and its corresponding translation product are known as the B7-H4 gene and B7-H4 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to embody the following preferred amino acid residues:

30 GIVAFIVLLLIMLIFL (SEQ ID NO: 1236). Polynucleotides encoding this polypeptide are also encompassed by the invention, as are antibodies that bind the polypeptide. The B7-H4 gene shares sequence homology with members of the B7

family of ligands (i.e., B7-1 (See Genbank Accession 507873)). These proteins and their corresponding receptors play vital roles in the growth, differentiation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production. Therefore, antagonists such as antibodies or small molecules directed against the B7-H4 gene are useful for treating T cell mediated immune system disorders. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention have uses, such as, for example, as a marker in linkage analysis for chromosome 1.

The translation product of this gene shares sequence homology with human poliovirus receptor precursors which are thought to be important in viral binding and uptake. The translation product of this gene also shares homology with a mouse member of the immunoglobulin superfamily, which is thought to be important in proper immune function (GENBANK: accession AF061260).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

ELSISISNVALADEGEYTCSTFTMPVRTAKSLVTVLGIPQKPIITGYKSSLREKD
TATLNCQSSGSKPAARLTWRKGDQELHGEPTRIQEDPNGKTFTVSSSVTFQVT
REDDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPDPPHPREGQKLLL
HCEGRGNPVPQQYLWEKEGSPPLKMTQESALIFPFLNKSDSGTYGCTATSN
MGSYKAYYTLNVND (SEQ ID NO:947),
ELSISISNVALADEGEYTCSTFTMPVRTAKSLVTVLGIPQKPIITGYKSSLREKD
TATLNCQSS (SEQ ID NO:948),
CQSSGSKPAARLTWRKGDQELHGEPTRIQEDPNGKTFTVSSSVTFQVTREDD
GASIVCSVNHESL (SEQ ID NO:949),
HESLKGADRSTSQRIEVLYTPTAMIRPDPPHPREGQKLLHCEGRGNPVPQQY
LWEKE (SEQ ID NO:950),
WEKEGSPPLKMTQESALIFPFLNKSDSGTYGCTATSNMGSYKAYYTLNVND
(SEQ ID NO:951), PSPVPSSSTYHAIIGGIVAFIVFLLIMLIFLGHY (SEQ ID
NO:952), and/or LIRHKGTYLTHEAKGSDDAPDADTAIINAEGGQSGGDDKK
EYFI (SEQ ID NO:953). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%,

90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

A splice variant of this gene has been identified which encodes a polypeptide lacking the following amino acid segment of SEQ ID NO: 361:

DGYWQEQDLELGLTAPLDEAISSTWSSPDMLASQ (SEQ ID NO: 1240). This splice variant was identified in clone HCE1K47, deposited in ATCC Deposit Accession No. PTA-2574 on October 5, 2000 and in ATCC Deposit Accession No. Unknown on February 16, 2001.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

NLSQDGYWQEQDLELGLTAPLDEAISSTWSSPDMLASQDSQP (SEQ ID NO: 1241), DGYWQEQDLELGLTAPLDEAISSTWSSPDMLASQ (SEQ ID NO: 1240), and/or NLSQDSQP (SEQ ID NO: 1242). In a further specific embodiment, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

MGAPAASLLLLLLFACCWAPGGANLSQDDSQPWTSDETVVAGGTVVLKCQ VKDHEDSSLQWS (SEQ ID NO: 1243). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed almost exclusively in human brain tissue.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve,

thirteen, fourteen, fifteen, sixteen, or all sixteen of the immunogenic epitopes of the extracellular portion of the B7-H4 protein shown in SEQ ID NO: 361 as residues:

Leu-26 to Asp-36, Gln-63 to Asp-71, Lys-87 to Gln-102, Gly-107 to Arg-116, Tyr-172 to Ala-182, Thr-198 to His-207, Glu-209 to Lys-220, Thr-233 to Gly-238, Glu-248 to Gln-259, Pro-273 to Gln-282, Glu-289 to Gln-297, Asn-324 to Thr-330, Val-350 to Pro-355, Ile-390 to Thr-395, Ala-401 to Ala-410, Glu-418 to Tyr-430.

Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides.

In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, one or more of the following amino acid sequences:

1.) The extracellular domain of the B7-H4 protein:

MGAPAASLLLLLLFACCWAPGGANLSQDGYWQEQLDELGLTAPLDEAISST
WSSPDMLASQDSQPWTSDETVVAGGTIVLKCQVKDHEDSSLQWSNPAQQT
LYFGEKRALRDNRIQLVTSTPHELSISISNVALADEGEYTCSTFTMPVRTAKSL
VTVLGIPQKPIITGYKSSLREKDTATLNCQSSGSKPAARLTWRKGDQELHGEP
TRIQEDPNGKTFTVSSSVTFQVTREDDGASIVCSVNHESLKGADRSTSQRIEVL
YTPTAMIRPDPPHPREGQKLLHCEGRGNPVPQQYLWEKEGSVPPLKMTQES
ALIFPFLNKSDSGTYGCTATSNMGSYKAYYTLNVNDPSPVPSSSSTYHAIIG
(SEQ ID NO: 1237);

2.) The mature extracellular domain of the B7-H4 protein:

NLSQDGYWQEQLDELGLTAPLDEAISSTVWSSPDMLASQDSQPWTSDETVV
AGGTIVLKCQVKDHEDSSLQWSNPAQQTLYFGEKRALRDNRIQLVTSTPHELS
ISISNVALADEGEYTCSTFTMPVRTAKSLVTVLGIPQKPIITGYKSSLREKDTA
TLNCQSSGSKPAARLTWRKGDQELHGEPTRIQEDPNGKTFTVSSSVTFQVTRE
DDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPDPPHPREGQKLLHCE
EGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCTATSNMG
SYKAYYTLNVNDPSPVPSSSSTYHAIIG (SEQ ID NO: 1238); and/or

3.) The anticipated leader sequence of the B7-H4 protein:

MGAPAASLLLLLLFACCWAPGGA (SEQ ID NO: 1239).

Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides.

Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature extracellular portion of the B7-H4 protein demonstrating functional activity (SEQ ID NO: 361). Polynucleotides encoding these polypeptides are also encompassed by the invention. By functional activity is meant, a polypeptide
5 fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H4 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H4 polypeptide for binding) to an anti-B7-H4 antibody],
10 immunogenicity (ability to generate antibody which binds to a B7-H4 polypeptide), ability to form multimers with B7-H4 polypeptides of the invention, and ability to bind to a receptor or ligand for a B7-H4 polypeptide.

Figures 3A-C show the nucleotide (SEQ ID NO: 123) and deduced amino acid sequence (SEQ ID NO: 361) corresponding to this gene.

15 Figure 4 shows an analysis of the amino acid sequence (SEQ ID NO: 361). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the
20 highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 4 are also represented in tabular form in Table 4.
25 The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figures 3A-3C, and Table 4: "Res": amino acid residue of SEQ ID NO: 361 and Figures 3A-3C; "Position": position of the corresponding residue within SEQ ID NO: 361 and Figures 3A-3C; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions -
30 Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-

Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

5 Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions,
10 alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 4 and/or Table 4, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data
15 presented in columns VIII, IX, XIII, and XIV of Table 4 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in
20 which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 4, but may, as shown in Table 4, be represented or identified by using tabular representations of the data presented in Figure 4. The DNA*STAR computer algorithm used to generate
25 Figure 4 (set on the original default parameters) was used to present the data in Figure 4 in a tabular format (See Table 4). The tabular format of the data in Figure 4 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide
30 sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 123, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least

about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 123. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 123. In this context "about" includes the particularly recited size, and sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 123, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxyl terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-432 where m is an integer from 2 to 426, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 361. More in particular, the invention provides

polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: G-2 to I-432; A-3 to I-432; P-4 to I-432; A-5 to I-432; A-6 to I-432; S-7 to I-432; L-8 to I-432; L-9 to I-432; L-10 to I-432; L-11 to I-432; L-12 to I-432; L-13 to I-432; L-14 to I-432; F-15 to I-432; A-16 to I-432; C-17 to I-432; C-18 to I-432; W-19 to I-432; A-20 to I-432; P-21 to I-432; G-22 to I-432; G-23 to I-432; A-24 to I-432; N-25 to I-432; L-26 to I-432; S-27 to I-432; Q-28 to I-432; D-29 to I-432; G-30 to I-432; Y-31 to I-432; W-32 to I-432; Q-33 to I-432; E-34 to I-432; Q-35 to I-432; D-36 to I-432; L-37 to I-432; E-38 to I-432; L-39 to I-432; G-40 to I-432; T-41 to I-432; L-42 to I-432; A-43 to I-432; P-44 to I-432; L-45 to I-432; D-46 to I-432; E-47 to I-432; A-48 to I-432; I-49 to I-432; S-50 to I-432; S-51 to I-432; T-52 to I-432; V-53 to I-432; W-54 to I-432; S-55 to I-432; S-56 to I-432; P-57 to I-432; D-58 to I-432; M-59 to I-432; L-60 to I-432; A-61 to I-432; S-62 to I-432; Q-63 to I-432; D-64 to I-432; S-65 to I-432; Q-66 to I-432; P-67 to I-432; W-68 to I-432; T-69 to I-432; S-70 to I-432; D-71 to I-432; E-72 to I-432; T-73 to I-432; V-74 to I-432; V-75 to I-432; A-76 to I-432; G-77 to I-432; G-78 to I-432; T-79 to I-432; V-80 to I-432; V-81 to I-432; L-82 to I-432; K-83 to I-432; C-84 to I-432; Q-85 to I-432; V-86 to I-432; K-87 to I-432; D-88 to I-432; H-89 to I-432; E-90 to I-432; D-91 to I-432; S-92 to I-432; S-93 to I-432; L-94 to I-432; Q-95 to I-432; W-96 to I-432; S-97 to I-432; N-98 to I-432; P-99 to I-432; A-100 to I-432; Q-101 to I-432; Q-102 to I-432; T-103 to I-432; L-104 to I-432; Y-105 to I-432; F-106 to I-432; G-107 to I-432; E-108 to I-432; K-109 to I-432; R-110 to I-432; A-111 to I-432; L-112 to I-432; R-113 to I-432; D-114 to I-432; N-115 to I-432; R-116 to I-432; I-117 to I-432; Q-118 to I-432; L-119 to I-432; V-120 to I-432; T-121 to I-432; S-122 to I-432; T-123 to I-432; P-124 to I-432; H-125 to I-432; E-126 to I-432; L-127 to I-432; S-128 to I-432; I-129 to I-432; S-130 to I-432; I-131 to I-432; S-132 to I-432; N-133 to I-432; V-134 to I-432; A-135 to I-432; L-136 to I-432; A-137 to I-432; D-138 to I-432; E-139 to I-432; G-140 to I-432; E-141 to I-432; Y-142 to I-432; T-143 to I-432; C-144 to I-432; S-145 to I-432; I-146 to I-432; F-147 to I-432; T-148 to I-432; M-149 to I-432; P-150 to I-432; V-151 to I-432; R-152 to I-432; T-153 to I-432; A-154 to I-432; K-155 to I-432; S-156 to I-432; L-157 to I-432; V-158 to I-432; T-159 to I-432; V-160 to I-432; L-161 to I-432; G-162 to I-432; I-163 to I-432; P-164 to I-432; Q-165 to I-432; K-166 to I-432; P-167 to I-432; I-168 to I-432; I-169 to I-432;

T-170 to I-432; G-171 to I-432; Y-172 to I-432; K-173 to I-432; S-174 to I-432; S-175 to I-432; L-176 to I-432; R-177 to I-432; E-178 to I-432; K-179 to I-432; D-180 to I-432; T-181 to I-432; A-182 to I-432; T-183 to I-432; L-184 to I-432; N-185 to I-432; C-186 to I-432; Q-187 to I-432; S-188 to I-432; S-189 to I-432; G-190 to I-432;
5 S-191 to I-432; K-192 to I-432; P-193 to I-432; A-194 to I-432; A-195 to I-432; R-196 to I-432; L-197 to I-432; T-198 to I-432; W-199 to I-432; R-200 to I-432; K-201 to I-432; G-202 to I-432; D-203 to I-432; Q-204 to I-432; E-205 to I-432; L-206 to I-432; H-207 to I-432; G-208 to I-432; E-209 to I-432; P-210 to I-432; T-211 to I-432; R-212 to I-432; I-213 to I-432; Q-214 to I-432; E-215 to I-432; D-216 to I-432; P-217 to I-432; N-218 to I-432; G-219 to I-432; K-220 to I-432; T-221 to I-432; F-222 to I-432; T-223 to I-432; V-224 to I-432; S-225 to I-432; S-226 to I-432; S-227 to I-432; V-228 to I-432; T-229 to I-432; F-230 to I-432; Q-231 to I-432; V-232 to I-432; T-233 to I-432; R-234 to I-432; E-235 to I-432; D-236 to I-432; D-237 to I-432; G-238 to I-432; A-239 to I-432; S-240 to I-432; I-241 to I-432; V-242 to I-432; C-243 to I-432; S-244 to I-432; V-245 to I-432; N-246 to I-432; H-247 to I-432; E-248 to I-432; S-249 to I-432; L-250 to I-432; K-251 to I-432; G-252 to I-432; A-253 to I-432; D-254 to I-432; R-255 to I-432; S-256 to I-432; T-257 to I-432; S-258 to I-432; Q-259 to I-432; R-260 to I-432; I-261 to I-432; E-262 to I-432; V-263 to I-432; L-264 to I-432; Y-265 to I-432; T-266 to I-432; P-267 to I-432; T-268 to I-432; A-269 to I-432;
20 M-270 to I-432; I-271 to I-432; R-272 to I-432; P-273 to I-432; D-274 to I-432; P-275 to I-432; P-276 to I-432; H-277 to I-432; P-278 to I-432; R-279 to I-432; E-280 to I-432; G-281 to I-432; Q-282 to I-432; K-283 to I-432; L-284 to I-432; L-285 to I-432; L-286 to I-432; H-287 to I-432; C-288 to I-432; E-289 to I-432; G-290 to I-432; R-291 to I-432; G-292 to I-432; N-293 to I-432; P-294 to I-432; V-295 to I-432; P-296 to I-432; Q-297 to I-432; Q-298 to I-432; Y-299 to I-432; L-300 to I-432; W-301 to I-432; E-302 to I-432; K-303 to I-432; E-304 to I-432; G-305 to I-432; S-306 to I-432; V-307 to I-432; P-308 to I-432; P-309 to I-432; L-310 to I-432; K-311 to I-432; M-312 to I-432; T-313 to I-432; Q-314 to I-432; E-315 to I-432; S-316 to I-432; A-317 to I-432; L-318 to I-432; I-319 to I-432; F-320 to I-432; P-321 to I-432; F-322 to I-432; L-323 to I-432; N-324 to I-432; K-325 to I-432; S-326 to I-432; D-327 to I-432; S-328 to I-432; G-329 to I-432; T-330 to I-432; Y-331 to I-432; G-332 to I-432; C-333 to I-432; T-334 to I-432; A-335 to I-432; T-336 to I-432; S-337 to I-432; N-

338 to I-432; M-339 to I-432; G-340 to I-432; S-341 to I-432; Y-342 to I-432; K-343 to I-432; A-344 to I-432; Y-345 to I-432; Y-346 to I-432; T-347 to I-432; L-348 to I-432; N-349 to I-432; V-350 to I-432; N-351 to I-432; D-352 to I-432; P-353 to I-432; S-354 to I-432; P-355 to I-432; V-356 to I-432; P-357 to I-432; S-358 to I-432; S-359 to I-432; S-360 to I-432; S-361 to I-432; T-362 to I-432; Y-363 to I-432; H-364 to I-432; A-365 to I-432; I-366 to I-432; I-367 to I-432; G-368 to I-432; G-369 to I-432; I-370 to I-432; V-371 to I-432; A-372 to I-432; F-373 to I-432; I-374 to I-432; V-375 to I-432; F-376 to I-432; L-377 to I-432; L-378 to I-432; L-379 to I-432; I-380 to I-432; M-381 to I-432; L-382 to I-432; I-383 to I-432; F-384 to I-432; L-385 to I-432; G-386 to I-432; H-387 to I-432; Y-388 to I-432; L-389 to I-432; I-390 to I-432; R-391 to I-432; H-392 to I-432; K-393 to I-432; G-394 to I-432; T-395 to I-432; Y-396 to I-432; L-397 to I-432; T-398 to I-432; H-399 to I-432; E-400 to I-432; A-401 to I-432; K-402 to I-432; G-403 to I-432; S-404 to I-432; D-405 to I-432; D-406 to I-432; A-407 to I-432; P-408 to I-432; D-409 to I-432; A-410 to I-432; D-411 to I-432; T-412 to I-432; A-413 to I-432; I-414 to I-432; I-415 to I-432; N-416 to I-432; A-417 to I-432; E-418 to I-432; G-419 to I-432; G-420 to I-432; Q-421 to I-432; S-422 to I-432; G-423 to I-432; G-424 to I-432; D-425 to I-432; D-426 to I-432; and/or K-427 to I-432 of SEQ ID NO: 361. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

20 Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to F-431; M-1 to Y-430; M-1 to E-429; M-1 to K-428; M-1 to K-427; M-1 to D-426; M-1 to D-425; M-1 to G-424; M-1 to G-423; M-1 to S-422; M-1 to Q-421; M-1 to G-420; M-1 to G-419; M-1 to E-418; M-1 to A-417; M-1 to N-416; M-1 to I-415; M-1 to I-414; M-1 to A-413; M-1 to T-412; M-1 to D-411; M-1 to A-410; M-1 to D-409; M-1 to P-408; M-1 to A-407; M-1 to D-406; M-1 to D-405; M-1 to S-404; M-1 to G-403; M-1 to K-402; M-1 to A-401; M-1 to E-400; M-1 to H-399; M-1 to T-398; M-1 to L-397; M-1 to Y-396; M-1 to T-395; M-1 to G-394; M-1 to K-393; M-1 to H-392; M-1 to R-391; M-1 to I-390; M-1 to L-389; M-1 to Y-388; M-1 to H-387; M-1 to G-386; M-1 to L-385; M-1 to F-384; M-1 to I-383; M-1 to L-382; M-1 to M-381; M-1 to I-380; M-1 to L-379; M-1 to L-378; M-1 to L-377; M-1 to F-376; M-1 to V-375; M-1 to I-374; M-1 to F-373; M-1 to A-

372; M-1 to V-371; M-1 to I-370; M-1 to G-369; M-1 to G-368; M-1 to I-367; M-1 to I-366; M-1 to A-365; M-1 to H-364; M-1 to Y-363; M-1 to T-362; M-1 to S-361; M-1 to S-360; M-1 to S-359; M-1 to S-358; M-1 to P-357; M-1 to V-356; M-1 to P-355; M-1 to S-354; M-1 to P-353; M-1 to D-352; M-1 to N-351; M-1 to V-350; M-1 to N-349; M-1 to L-348; M-1 to T-347; M-1 to Y-346; M-1 to Y-345; M-1 to A-344; M-1 to K-343; M-1 to Y-342; M-1 to S-341; M-1 to G-340; M-1 to M-339; M-1 to N-338; M-1 to S-337; M-1 to T-336; M-1 to A-335; M-1 to T-334; M-1 to C-333; M-1 to G-332; M-1 to Y-331; M-1 to T-330; M-1 to G-329; M-1 to S-328; M-1 to D-327; M-1 to S-326; M-1 to K-325; M-1 to N-324; M-1 to L-323; M-1 to F-322; M-1 to P-321; M-1 to F-320; M-1 to I-319; M-1 to L-318; M-1 to A-317; M-1 to S-316; M-1 to E-315; M-1 to Q-314; M-1 to T-313; M-1 to M-312; M-1 to K-311; M-1 to L-310; M-1 to P-309; M-1 to P-308; M-1 to V-307; M-1 to S-306; M-1 to G-305; M-1 to E-304; M-1 to K-303; M-1 to E-302; M-1 to W-301; M-1 to L-300; M-1 to Y-299; M-1 to Q-298; M-1 to Q-297; M-1 to P-296; M-1 to V-295; M-1 to P-294; M-1 to N-293; M-1 to G-292; M-1 to R-291; M-1 to G-290; M-1 to E-289; M-1 to C-288; M-1 to H-287; M-1 to L-286; M-1 to L-285; M-1 to L-284; M-1 to K-283; M-1 to Q-282; M-1 to G-281; M-1 to E-280; M-1 to R-279; M-1 to P-278; M-1 to H-277; M-1 to P-276; M-1 to P-275; M-1 to D-274; M-1 to P-273; M-1 to R-272; M-1 to I-271; M-1 to M-270; M-1 to A-269; M-1 to T-268; M-1 to P-267; M-1 to T-266; M-1 to Y-265; M-1 to L-264; M-1 to V-263; M-1 to E-262; M-1 to I-261; M-1 to R-260; M-1 to Q-259; M-1 to S-258; M-1 to T-257; M-1 to S-256; M-1 to R-255; M-1 to D-254; M-1 to A-253; M-1 to G-252; M-1 to K-251; M-1 to L-250; M-1 to S-249; M-1 to E-248; M-1 to H-247; M-1 to N-246; M-1 to V-245; M-1 to S-244; M-1 to C-243; M-1 to V-242; M-1 to I-241; M-1 to S-240; M-1 to A-239; M-1 to G-238; M-1 to D-237; M-1 to D-236; M-1 to E-235; M-1 to R-234; M-1 to T-233; M-1 to V-232; M-1 to Q-231; M-1 to F-230; M-1 to T-229; M-1 to V-228; M-1 to S-227; M-1 to S-226; M-1 to S-225; M-1 to V-224; M-1 to T-223; M-1 to F-222; M-1 to T-221; M-1 to K-220; M-1 to G-219; M-1 to N-218; M-1 to P-217; M-1 to D-216; M-1 to E-215; M-1 to Q-214; M-1 to I-213; M-1 to R-212; M-1 to T-211; M-1 to P-210; M-1 to E-209; M-1 to G-208; M-1 to H-207; M-1 to L-206; M-1 to E-205; M-1 to Q-204; M-1 to D-203; M-1 to G-202; M-1 to K-201; M-1 to R-200; M-1 to W-199; M-1 to T-198; M-1 to L-197; M-1 to R-196; M-1 to A-195; M-1 to A-194; M-1 to P-193; M-1 to K-192; M-1 to S-191; M-1

to G-190; M-1 to S-189; M-1 to S-188; M-1 to Q-187; M-1 to C-186; M-1 to N-185; M-1 to L-184; M-1 to T-183; M-1 to A-182; M-1 to T-181; M-1 to D-180; M-1 to K-179; M-1 to E-178; M-1 to R-177; M-1 to L-176; M-1 to S-175; M-1 to S-174; M-1 to K-173; M-1 to Y-172; M-1 to G-171; M-1 to T-170; M-1 to I-169; M-1 to I-168;

5 M-1 to P-167; M-1 to K-166; M-1 to Q-165; M-1 to P-164; M-1 to I-163; M-1 to G-162; M-1 to L-161; M-1 to V-160; M-1 to T-159; M-1 to V-158; M-1 to L-157; M-1 to S-156; M-1 to K-155; M-1 to A-154; M-1 to T-153; M-1 to R-152; M-1 to V-151; M-1 to P-150; M-1 to M-149; M-1 to T-148; M-1 to F-147; M-1 to I-146; M-1 to S-145; M-1 to C-144; M-1 to T-143; M-1 to Y-142; M-1 to E-141; M-1 to G-140; M-1

10 to E-139; M-1 to D-138; M-1 to A-137; M-1 to L-136; M-1 to A-135; M-1 to V-134; M-1 to N-133; M-1 to S-132; M-1 to I-131; M-1 to S-130; M-1 to I-129; M-1 to S-128; M-1 to L-127; M-1 to E-126; M-1 to H-125; M-1 to P-124; M-1 to T-123; M-1 to S-122; M-1 to T-121; M-1 to V-120; M-1 to L-119; M-1 to Q-118; M-1 to I-117; M-1 to R-116; M-1 to N-115; M-1 to D-114; M-1 to R-113; M-1 to L-112; M-1 to A-

15 111; M-1 to R-110; M-1 to K-109; M-1 to E-108; M-1 to G-107; M-1 to F-106; M-1 to Y-105; M-1 to L-104; M-1 to T-103; M-1 to Q-102; M-1 to Q-101; M-1 to A-100; M-1 to P-99; M-1 to N-98; M-1 to S-97; M-1 to W-96; M-1 to Q-95; M-1 to L-94; M-1 to S-93; M-1 to S-92; M-1 to D-91; M-1 to E-90; M-1 to H-89; M-1 to D-88; M-1 to K-87; M-1 to V-86; M-1 to Q-85; M-1 to C-84; M-1 to K-83; M-1 to L-82; M-1 to

20 V-81; M-1 to V-80; M-1 to T-79; M-1 to G-78; M-1 to G-77; M-1 to A-76; M-1 to V-75; M-1 to V-74; M-1 to T-73; M-1 to E-72; M-1 to D-71; M-1 to S-70; M-1 to T-69; M-1 to W-68; M-1 to P-67; M-1 to Q-66; M-1 to S-65; M-1 to D-64; M-1 to Q-63; M-1 to S-62; M-1 to A-61; M-1 to L-60; M-1 to M-59; M-1 to D-58; M-1 to P-57; M-1 to S-56; M-1 to S-55; M-1 to W-54; M-1 to V-53; M-1 to T-52; M-1 to S-51; M-1

25 to S-50; M-1 to I-49; M-1 to A-48; M-1 to E-47; M-1 to D-46; M-1 to L-45; M-1 to P-44; M-1 to A-43; M-1 to L-42; M-1 to T-41; M-1 to G-40; M-1 to L-39; M-1 to E-38; M-1 to L-37; M-1 to D-36; M-1 to Q-35; M-1 to E-34; M-1 to Q-33; M-1 to W-32; M-1 to Y-31; M-1 to G-30; M-1 to D-29; M-1 to Q-28; M-1 to S-27; M-1 to L-26; M-1 to N-25; M-1 to A-24; M-1 to G-23; M-1 to G-22; M-1 to P-21; M-1 to A-20; M-

30 1 to W-19; M-1 to C-18; M-1 to C-17; M-1 to A-16; M-1 to F-15; M-1 to L-14; M-1 to L-13; M-1 to L-12; M-1 to L-11; M-1 to L-10; M-1 to L-9; M-1 to L-8; and/or M-1

to S-7 of SEQ ID NO: 361. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response. Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxyl terminus of the amino acid sequence of the polypeptide shown in Figures 3A-3C (SEQ ID NO: 361), as described by the general formula 1-n, where n is an integer from 6 to 432, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 361.

More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature extracellular portion of the B7-H4 protein (SEQ ID NO: 1238): L-26 to G-368; S-27 to G-368; Q-28 to G-368; D-29 to G-368; G-30 to G-368; Y-31 to G-368; W-32 to G-368; Q-33 to G-368; E-34 to G-368; Q-35 to G-368; D-36 to G-368; L-37 to G-368; E-38 to G-368; L-39 to G-368; G-40 to G-368; T-41 to G-368; L-42 to G-368; A-43 to G-368; P-44 to G-368; L-45 to G-368; D-46 to G-368; E-47 to G-368; A-48 to G-368; I-49 to G-368; S-50 to G-368; S-51 to G-368; T-52 to G-368; V-53 to G-368; W-54 to G-368; S-55 to G-368; S-56 to G-368; P-57 to G-368; D-58 to G-368; M-59 to G-368; L-60 to G-

368; A-61 to G-368; S-62 to G-368; Q-63 to G-368; D-64 to G-368; S-65 to G-368;
Q-66 to G-368; P-67 to G-368; W-68 to G-368; T-69 to G-368; S-70 to G-368; D-71
to G-368; E-72 to G-368; T-73 to G-368; V-74 to G-368; V-75 to G-368; A-76 to G-
368; G-77 to G-368; G-78 to G-368; T-79 to G-368; V-80 to G-368; V-81 to G-368;
5 L-82 to G-368; K-83 to G-368; C-84 to G-368; Q-85 to G-368; V-86 to G-368; K-87
to G-368; D-88 to G-368; H-89 to G-368; E-90 to G-368; D-91 to G-368; S-92 to G-
368; S-93 to G-368; L-94 to G-368; Q-95 to G-368; W-96 to G-368; S-97 to G-368;
N-98 to G-368; P-99 to G-368; A-100 to G-368; Q-101 to G-368; Q-102 to G-368; T-
103 to G-368; L-104 to G-368; Y-105 to G-368; F-106 to G-368; G-107 to G-368; E-
10 108 to G-368; K-109 to G-368; R-110 to G-368; A-111 to G-368; L-112 to G-368; R-
113 to G-368; D-114 to G-368; N-115 to G-368; R-116 to G-368; I-117 to G-368; Q-
118 to G-368; L-119 to G-368; V-120 to G-368; T-121 to G-368; S-122 to G-368; T-
123 to G-368; P-124 to G-368; H-125 to G-368; E-126 to G-368; L-127 to G-368; S-
128 to G-368; I-129 to G-368; S-130 to G-368; I-131 to G-368; S-132 to G-368; N-
15 133 to G-368; V-134 to G-368; A-135 to G-368; L-136 to G-368; A-137 to G-368; D-
138 to G-368; E-139 to G-368; G-140 to G-368; E-141 to G-368; Y-142 to G-368; T-
143 to G-368; C-144 to G-368; S-145 to G-368; I-146 to G-368; F-147 to G-368; T-
148 to G-368; M-149 to G-368; P-150 to G-368; V-151 to G-368; R-152 to G-368; T-
153 to G-368; A-154 to G-368; K-155 to G-368; S-156 to G-368; L-157 to G-368; V-
20 158 to G-368; T-159 to G-368; V-160 to G-368; L-161 to G-368; G-162 to G-368; I-
163 to G-368; P-164 to G-368; Q-165 to G-368; K-166 to G-368; P-167 to G-368; I-
168 to G-368; I-169 to G-368; T-170 to G-368; G-171 to G-368; Y-172 to G-368; K-
173 to G-368; S-174 to G-368; S-175 to G-368; L-176 to G-368; R-177 to G-368; E-
178 to G-368; K-179 to G-368; D-180 to G-368; T-181 to G-368; A-182 to G-368; T-
25 183 to G-368; L-184 to G-368; N-185 to G-368; C-186 to G-368; Q-187 to G-368; S-
188 to G-368; S-189 to G-368; G-190 to G-368; S-191 to G-368; K-192 to G-368; P-
193 to G-368; A-194 to G-368; A-195 to G-368; R-196 to G-368; L-197 to G-368; T-
198 to G-368; W-199 to G-368; R-200 to G-368; K-201 to G-368; G-202 to G-368;
D-203 to G-368; Q-204 to G-368; E-205 to G-368; L-206 to G-368; H-207 to G-368;
30 G-208 to G-368; E-209 to G-368; P-210 to G-368; T-211 to G-368; R-212 to G-368;
I-213 to G-368; Q-214 to G-368; E-215 to G-368; D-216 to G-368; P-217 to G-368;
N-218 to G-368; G-219 to G-368; K-220 to G-368; T-221 to G-368; F-222 to G-368;

T-223 to G-368; V-224 to G-368; S-225 to G-368; S-226 to G-368; S-227 to G-368;
V-228 to G-368; T-229 to G-368; F-230 to G-368; Q-231 to G-368; V-232 to G-368;
T-233 to G-368; R-234 to G-368; E-235 to G-368; D-236 to G-368; D-237 to G-368;
G-238 to G-368; A-239 to G-368; S-240 to G-368; I-241 to G-368; V-242 to G-368;
5 C-243 to G-368; S-244 to G-368; V-245 to G-368; N-246 to G-368; H-247 to G-368;
E-248 to G-368; S-249 to G-368; L-250 to G-368; K-251 to G-368; G-252 to G-368;
A-253 to G-368; D-254 to G-368; R-255 to G-368; S-256 to G-368; T-257 to G-368;
S-258 to G-368; Q-259 to G-368; R-260 to G-368; I-261 to G-368; E-262 to G-368;
V-263 to G-368; L-264 to G-368; Y-265 to G-368; T-266 to G-368; P-267 to G-368;
10 T-268 to G-368; A-269 to G-368; M-270 to G-368; I-271 to G-368; R-272 to G-368;
P-273 to G-368; D-274 to G-368; P-275 to G-368; P-276 to G-368; H-277 to G-368;
P-278 to G-368; R-279 to G-368; E-280 to G-368; G-281 to G-368; Q-282 to G-368;
K-283 to G-368; L-284 to G-368; L-285 to G-368; L-286 to G-368; H-287 to G-368;
C-288 to G-368; E-289 to G-368; G-290 to G-368; R-291 to G-368; G-292 to G-368;
15 N-293 to G-368; P-294 to G-368; V-295 to G-368; P-296 to G-368; Q-297 to G-368;
Q-298 to G-368; Y-299 to G-368; L-300 to G-368; W-301 to G-368; E-302 to G-368;
K-303 to G-368; E-304 to G-368; G-305 to G-368; S-306 to G-368; V-307 to G-368;
P-308 to G-368; P-309 to G-368; L-310 to G-368; K-311 to G-368; M-312 to G-368;
T-313 to G-368; Q-314 to G-368; E-315 to G-368; S-316 to G-368; A-317 to G-368;
20 L-318 to G-368; I-319 to G-368; F-320 to G-368; P-321 to G-368; F-322 to G-368; L-
323 to G-368; N-324 to G-368; K-325 to G-368; S-326 to G-368; D-327 to G-368; S-
328 to G-368; G-329 to G-368; T-330 to G-368; Y-331 to G-368; G-332 to G-368; C-
333 to G-368; T-334 to G-368; A-335 to G-368; T-336 to G-368; S-337 to G-368; N-
338 to G-368; M-339 to G-368; G-340 to G-368; S-341 to G-368; Y-342 to G-368;
25 K-343 to G-368; A-344 to G-368; Y-345 to G-368; Y-346 to G-368; T-347 to G-368;
L-348 to G-368; N-349 to G-368; V-350 to G-368; N-351 to G-368; D-352 to G-368;
P-353 to G-368; S-354 to G-368; P-355 to G-368; V-356 to G-368; P-357 to G-368;
S-358 to G-368; S-359 to G-368; S-360 to G-368; S-361 to G-368; T-362 to G-368;
and/or Y-363 to G-368 of SEQ ID NO: 1238. Polypeptides encoded by these
30 polynucleotides are also encompassed by the invention.

Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the

group of C-terminal deletions of the mature extracellular portion of the B7-H4 protein (SEQ ID NO: 1238): N-25 to I-367; N-25 to I-366; N-25 to A-365; N-25 to H-364; N-25 to Y-363; N-25 to T-362; N-25 to S-361; N-25 to S-360; N-25 to S-359; N-25 to S-358; N-25 to P-357; N-25 to V-356; N-25 to P-355; N-25 to S-354; N-25 to P-353; 5 N-25 to D-352; N-25 to N-351; N-25 to V-350; N-25 to N-349; N-25 to L-348; N-25 to T-347; N-25 to Y-346; N-25 to Y-345; N-25 to A-344; N-25 to K-343; N-25 to Y-342; N-25 to S-341; N-25 to G-340; N-25 to M-339; N-25 to N-338; N-25 to S-337; N-25 to T-336; N-25 to A-335; N-25 to T-334; N-25 to C-333; N-25 to G-332; N-25 to Y-331; N-25 to T-330; N-25 to G-329; N-25 to S-328; N-25 to D-327; N-25 to S-10 326; N-25 to K-325; N-25 to N-324; N-25 to L-323; N-25 to F-322; N-25 to P-321; N-25 to F-320; N-25 to I-319; N-25 to L-318; N-25 to A-317; N-25 to S-316; N-25 to E-315; N-25 to Q-314; N-25 to T-313; N-25 to M-312; N-25 to K-311; N-25 to L-310; N-25 to P-309; N-25 to P-308; N-25 to V-307; N-25 to S-306; N-25 to G-305; N-25 to E-304; N-25 to K-303; N-25 to E-302; N-25 to W-301; N-25 to L-300; N-25 15 to Y-299; N-25 to Q-298; N-25 to Q-297; N-25 to P-296; N-25 to V-295; N-25 to P-294; N-25 to N-293; N-25 to G-292; N-25 to R-291; N-25 to G-290; N-25 to E-289; N-25 to C-288; N-25 to H-287; N-25 to L-286; N-25 to L-285; N-25 to L-284; N-25 to K-283; N-25 to Q-282; N-25 to G-281; N-25 to E-280; N-25 to R-279; N-25 to P-278; N-25 to H-277; N-25 to P-276; N-25 to P-275; N-25 to D-274; N-25 to P-273; 20 N-25 to R-272; N-25 to I-271; N-25 to M-270; N-25 to A-269; N-25 to T-268; N-25 to P-267; N-25 to T-266; N-25 to Y-265; N-25 to L-264; N-25 to V-263; N-25 to E-262; N-25 to I-261; N-25 to R-260; N-25 to Q-259; N-25 to S-258; N-25 to T-257; N-25 to S-256; N-25 to R-255; N-25 to D-254; N-25 to A-253; N-25 to G-252; N-25 to K-251; N-25 to L-250; N-25 to S-249; N-25 to E-248; N-25 to H-247; N-25 to N-246; 25 N-25 to V-245; N-25 to S-244; N-25 to C-243; N-25 to V-242; N-25 to I-241; N-25 to S-240; N-25 to A-239; N-25 to G-238; N-25 to D-237; N-25 to D-236; N-25 to E-235; N-25 to R-234; N-25 to T-233; N-25 to V-232; N-25 to Q-231; N-25 to F-230; N-25 to T-229; N-25 to V-228; N-25 to S-227; N-25 to S-226; N-25 to S-225; N-25 to V-224; N-25 to T-223; N-25 to F-222; N-25 to T-221; N-25 to K-220; N-25 to G-219; 30 N-25 to N-218; N-25 to P-217; N-25 to D-216; N-25 to E-215; N-25 to Q-214; N-25 to I-213; N-25 to R-212; N-25 to T-211; N-25 to P-210; N-25 to E-209; N-25 to G-208; N-25 to H-207; N-25 to L-206; N-25 to E-205; N-25 to Q-204; N-25 to D-203;

N-25 to G-202; N-25 to K-201; N-25 to R-200; N-25 to W-199; N-25 to T-198; N-25 to L-197; N-25 to R-196; N-25 to A-195; N-25 to A-194; N-25 to P-193; N-25 to K-192; N-25 to S-191; N-25 to G-190; N-25 to S-189; N-25 to S-188; N-25 to Q-187; N-25 to C-186; N-25 to N-185; N-25 to L-184; N-25 to T-183; N-25 to A-182; N-25 to T-181; N-25 to D-180; N-25 to K-179; N-25 to E-178; N-25 to R-177; N-25 to L-176; N-25 to S-175; N-25 to S-174; N-25 to K-173; N-25 to Y-172; N-25 to G-171; N-25 to T-170; N-25 to I-169; N-25 to I-168; N-25 to P-167; N-25 to K-166; N-25 to Q-165; N-25 to P-164; N-25 to I-163; N-25 to G-162; N-25 to L-161; N-25 to V-160; N-25 to T-159; N-25 to V-158; N-25 to L-157; N-25 to S-156; N-25 to K-155; N-25 to A-154; N-25 to T-153; N-25 to R-152; N-25 to V-151; N-25 to P-150; N-25 to M-149; N-25 to T-148; N-25 to F-147; N-25 to I-146; N-25 to S-145; N-25 to C-144; N-25 to T-143; N-25 to Y-142; N-25 to E-141; N-25 to G-140; N-25 to E-139; N-25 to D-138; N-25 to A-137; N-25 to L-136; N-25 to A-135; N-25 to V-134; N-25 to N-133; N-25 to S-132; N-25 to I-131; N-25 to S-130; N-25 to I-129; N-25 to S-128; N-25 to L-127; N-25 to E-126; N-25 to H-125; N-25 to P-124; N-25 to T-123; N-25 to S-122; N-25 to T-121; N-25 to V-120; N-25 to L-119; N-25 to Q-118; N-25 to I-117; N-25 to R-116; N-25 to N-115; N-25 to D-114; N-25 to R-113; N-25 to L-112; N-25 to A-111; N-25 to R-110; N-25 to K-109; N-25 to E-108; N-25 to G-107; N-25 to F-106; N-25 to Y-105; N-25 to L-104; N-25 to T-103; N-25 to Q-102; N-25 to Q-101; N-25 to A-100; N-25 to P-99; N-25 to N-98; N-25 to S-97; N-25 to W-96; N-25 to Q-95; N-25 to L-94; N-25 to S-93; N-25 to S-92; N-25 to D-91; N-25 to E-90; N-25 to H-89; N-25 to D-88; N-25 to K-87; N-25 to V-86; N-25 to Q-85; N-25 to C-84; N-25 to K-83; N-25 to L-82; N-25 to V-81; N-25 to V-80; N-25 to T-79; N-25 to G-78; N-25 to G-77; N-25 to A-76; N-25 to V-75; N-25 to V-74; N-25 to T-73; N-25 to E-72; N-25 to D-71; N-25 to S-70; N-25 to T-69; N-25 to W-68; N-25 to P-67; N-25 to Q-66; N-25 to S-65; N-25 to D-64; N-25 to Q-63; N-25 to S-62; N-25 to A-61; N-25 to L-60; N-25 to M-59; N-25 to D-58; N-25 to P-57; N-25 to S-56; N-25 to S-55; N-25 to W-54; N-25 to V-53; N-25 to T-52; N-25 to S-51; N-25 to S-50; N-25 to I-49; N-25 to A-48; N-25 to E-47; N-25 to D-46; N-25 to L-45; N-25 to P-44; N-25 to A-43; N-25 to L-42; N-25 to T-41; N-25 to G-40; N-25 to L-39; N-25 to E-38; N-25 to L-37; N-25 to D-36; N-25 to Q-35; N-25 to E-34; N-25 to Q-33; N-25 to W-32; and/or

N-25 to Y-31 of SEQ ID NO: 1238. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 361, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit Nos. 209007 (deposited on April 28, 1997) and 209083 (deposited on May 29, 1997), where this portion excludes any integer of amino acid residues from 1 to about 228 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit Nos. 209007 and 209083, or any integer of amino acid residues from 1 to about 228 amino acids from the carboxyl terminus, or any combination of the above amino terminal and carboxyl terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Nos. 209007 and 209083. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of CNS and/or immune system tissue(s) or cell type(s)

present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells and/or neutrophils, susceptibility to viral disease and diseases of the CNS, especially cancers of that system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H4 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activities as are disclosed herein (e.g., T cell modulated activities).

For a number of disorders of the above tissues or cells, particularly of the immune system and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The homology to members of the B7 family of ligands indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells and/or neutrophils. In particular, the translation product of the B7-H4 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines.

More generally, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as

an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

The tissue distribution and homology to poliovirus receptor precursors suggests that the protein product of this clone would be useful for the treatment and prevention of diseases that involve the binding and uptake of virus particles for infection. It might also be helpful in genetic therapy where the goal is to insert foreign DNA into infected cells. With the help of this protein, the binding and uptake of this foreign DNA might be aided. In addition, it is expected that over expression of this gene will indicate abnormalities involving the CNS, particularly cancers of that system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 123 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2523 of SEQ ID NO: 123, b is an integer of 15 to 2537, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 123

FEATURES OF PROTEIN ENCODED BY GENE NO: 114

The translation product of this gene shares sequence homology with YO87_CAEEL hypothetical 28.5 KD protein ZK1236.7 in chromosome III of *Caenorhabditis elegans* in addition to alpha-1 collagen type III (See Genbank Accession No. gi|537432). In specific embodiments, polypeptides of the invention comprise, or alternatively

5 consists of, an amino acid sequence selected from the group:

VPELPDRVHQLHQA VQGICALGRPGFPGGPTHSGHHKSHPGPAGGDYNRCDR
PGQVHLHNPRGTGRRGQLHPTAGPGVHRRACPSQQLPHRLGPGVPCPSPSLT
PVLPSWTQSWCGLPGYTSSS (SEQ ID NO:954),
VHQLHQA VQGICALGRPGFPGG (SEQ ID NO:955),

10 PTHSGHHKSHPGPAGGDYNRCDRPGQVHLHNPRGTGRRGQLH (SEQ ID
NO:956), and/or

LHPTAGPGVHRRACPSQQLPHRLGPGVPCPSPSLTPVLPSWTQSWCGLPGYTSS
(SEQ ID NO:957). Moreover, fragments and variants of these polypeptides (such
as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
15 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
encoded by the polynucleotide which hybridizes, under stringent conditions, to the
polynucleotide encoding these polypeptides) are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
invention. Polynucleotides encoding these polypeptides are also encompassed by the
20 invention.

This gene is expressed primarily in brain cells, and to a lesser extent in activated B and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

25 and for diagnosis of diseases and conditions which include, but are not limited to, neurodegeneration and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and immune systems,

30 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

- 5 NO: 362 as residues: Glu-34 to Glu-39, Gly-51 to Ser-72, Ala-88 to Glu-93, Gln-100 to Val-105.

The tissue distribution in brain cells, combined with the homology to YO87_CAEEL hypothetical 28.5 KD protein ZK1236.7 in chromosome III of *Caenorhabditis elegans* as well as to a conserved alpha-1 collagen type III protein indicates that the protein product of this gene is useful for the detection and treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorders. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:124 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1376 of SEQ ID NO:124, b is an integer of 15 to 1390, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 115

The translation product of this gene shares sequence homology with alpha 3 type IX collagen, which is thought to be important in hyaline cartilage formation via its ability to uptake inorganic sulfate by cells (See Genbank Accession No. gi|975657).

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- SLRRPRSAAXQTLTTLSSVSSASSALPGSREPCDPRAPPPRSGSAASCCSCC
 CSCPRRRAPLRSPRGSKRRIRQREVVDLYNGMCLQGPAGVPGRDGPANGI
 PGTPGIPGRDGFKEGKEGCELRSESWTPNYKQCSWSSLNYGIDLKIAECT
 10 FTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECGSLPIEAIYLDQ
 GSPEMNSTINIHRSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNS
 VSRIIIIEELPK (SEQ ID NO:958),
 SLRRPRSAAXQTLTTLSSVSSASSALPGSREPCDPRAPPPRSGSAASCCSCC
 CSCPRR (SEQ ID NO:959),
 15 RAPLRSPRGSKRRIRQREVVDLYNGMCLQGPAGVPGRDGPANGIPGTPGI
 (SEQ ID NO:960),
 TPGIPGRDGFKEGKEGCELRSESWTPNYKQCSWSSLNYGIDLKIAECTF
 (SEQ ID NO:961),
 FTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECGSLPIEAIYLDQ
 20 GSPEMNSTINIHR (SEQ ID NO:962), and/or
 RTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIIEELPK
 (SEQ ID NO:963). Moreover, fragments and variants of these polypeptides (such as,
 for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
 25 encoded by the polynucleotide which hybridizes, under stringent conditions, to the
 polynucleotide encoding these polypeptides) are encompassed by the invention.
 Antibodies that bind polypeptides of the invention are also encompassed by the
 invention. Polynucleotides encoding these polypeptides are also encompassed by the
 invention.
- 30 This gene is expressed primarily in smooth muscle, and to a lesser extent in
 synovial tissue.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, dwarfism, spinal deformation, and specific joint abnormalities as well as

5 chondrodysplasias, i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid and autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. muscle, synovial tissues, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard

15 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in smooth muscle, and homology to alpha 3 type IX collagen indicates that the protein product of this gene is useful for the treatment and diagnosis of diseases associated with the mutation in this gene which leads to the

20 many different types of chondrodysplasias. By the use of this product, the abnormal growth and development of bones of the limbs and spine could be detected or treated *in utero*, since the protein or polypeptides thereof could affect epithelial cells early in development, and later the chondrocytes of the developing craniofacial structure. In addition, the expression of this gene product in synovium would suggest a role in the

25 detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and

30 specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Moreover, the expression within smooth muscle

indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, detection, and/or prevention of a variety of vascular disorders, which include, but are not limited to, atherosclerosis, embolism, stroke, aneurysm, or microvascular disease. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:125 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1274 of SEQ ID NO:125, b is an integer of 15 to 1288, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 116

The translation product of this gene shares sequence homology with retrovirus-related reverse transcriptase, which is thought to be important in viral replication.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: TKKENCRPASLMNIDTKILNKILMNQ (SEQ ID NO:964). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are

also encompassed by the invention. (See Genbank Accession No. pir|A25313|GNHUL1).

This gene is expressed primarily in human meningioma.

Polynucleotides and polypeptides of the invention are useful as reagents for
5 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
retroviral diseases such as AIDS, and possibly certain cancers due to transactivation
of latent cell division genes. Similarly, polypeptides and antibodies directed to these
polypeptides are useful in providing immunological probes for differential
10 identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the immune system, expression of this gene at
significantly higher or lower levels may be routinely detected in certain tissues or cell
types (e.g. meningioma, cancerous and wounded tissues) or bodily fluids (e.g., lymph,
serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
15 taken from an individual having such a disorder, relative to the standard gene
expression level, i.e., the expression level in healthy tissue or bodily fluid from an
individual not having the disorder.

The tissue distribution in human meningioma, combined with the homology to
a retrovirus-related reverse transcriptase indicates that the protein product of this gene
20 is useful for the detection and treatment of diseases and conditions associated with
retroviral infection, since a functional reverse transcriptase (RT) or RT-like molecule
is an integral component of the retroviral life cycle. Protein, as well as, antibodies
directed against the protein may show utility as a tumor marker and/or
immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly
available and accessible through sequence databases. Some of these sequences are
related to SEQ ID NO:126 and may have been publicly available prior to conception
of the present invention. Preferably, such related polynucleotides are specifically
excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or
more polynucleotides comprising a nucleotide sequence described by the general
formula of a-b, where a is any integer between 1 to 1503 of SEQ ID NO:126, b is an

integer of 15 to 1517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 117

The translation product of this gene shares sequence homology with an unknown gene from *C. elegans*, as well as weak homolog with mammalian metaxin, a gene contiguous to both thrombospondin 3 and glucocerebrosidase, and is known to
 10 be required for embryonic development. Recently another group cloned and sequenced this gene from humans, naming it metaxin 2. It is thought that metaxin 1 and metaxin 2 interact, and are associated with the mammalian mitochondrial outer membrane (See Genbank Accession No. AF053551).

In specific embodiments, polypeptides of the invention comprise, or alternatively
 15 consists of, an amino acid sequence selected from the group:
 MCNLPIKVVCRANA EYMSPSGKVPXXHVG NQVVSELGPIVQFVKAKGHSLS
 DGLEEVQKAEMKAYMELVNNMLLTAELYLQWCDEATVGXITHXRYGSPYP
 WPLXHILAYQKQWEVKRKXKAIGWGKKTL DQVLEDVDQCCQALSQRLGTQ
 PYFFNKQPTELDALVFGHLYTILTTQLTNDELSEKVKNYSNLLAFCRRIEQHY
 20 FED RGKGRLS (SEQ ID NO:965),
 MCNLPIKVVCRANA EYMSPSGKVPXXHVG NQVVSELGPIVQFVK (SEQ ID
 NO:966), FVKAKGHSLS DGLEEVQKAEMKAYMELVNNMLLTAELYLQWCDE
 (SEQ ID NO:967), LQWCDEATVGXITHXRYGSPYPWP
 LXHILAYQKQWEVKRKXKAIGWGKKTL (SEQ ID NO:968),
 25 DQVLEDVDQCCQ ALSQRLGTQPYFFNKQPTELDALVFGHLYTI (SEQ ID
 NO:969), and/or LTTQLTNDELSEKVKNYSNLLAFCRRIEQHYFEDRGKGRLS
 (SEQ ID NO:970). Moreover, fragments and variants of these polypeptides (such as,
 for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
 30 encoded by the polynucleotide which hybridizes, under stringent conditions, to the
 polynucleotide encoding these polypeptides) are encompassed by the invention.
 Antibodies that bind polypeptides of the invention are also encompassed by the

invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. gi|1326108).

The gene encoding the disclosed cDNA is thought to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in
5 linkage analysis for chromosome 2.

This gene is expressed primarily in fetal tissues, and to a lesser extent in hematopoietic cells and tissues, including spleen, monocytes, and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
10 and for diagnosis of diseases and conditions which include, but are not limited to, cancer; lymphoproliferative disorders; inflammation; chondrosarcoma, and Gaucher disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
15 particularly of the hematopoietic and embryonic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, fetal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of cancer and other proliferative disorders. Moreover, this protein may play a role in the regulation of cellular
25 division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and survival of hematopoietic cell lineages. Thus, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor
30 cells. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:127 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1059 of SEQ ID NO:127, b is an integer of 15 to 1073, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 118

The translation product of this gene shares sequence homology with reverse transcriptase, which is important in the synthesis of a cDNA chain from an RNA molecule, and is a method whereby the infecting RNA chains of retroviruses are transcribed into their DNA complements.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: MXXXNSHITIFTLNVNGLNAPNERHRLANWIQSQDQVCCIQETHLTGRDTHR LKIKGWRKIYQANGKQKK (SEQ ID NO:971), FTLNVNGLNAPNERHRLANWIQSQDQVC (SEQ ID NO:972), THLTGRDTHRLKIKGWR (SEQ ID NO:973), and/or GWRKIYQANGKQKK (SEQ ID NO:974). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. gi|2072964).

This gene is expressed primarily in skin, and to a lesser extent in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers; hematopoietic disorders; inflammation; disorders of immune surveillance. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermis and/or hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. skin, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in skin, combined with the homology to a reverse transcriptase indicates that the protein product of this gene is useful for cancer therapy, particularly of the integumentary system. Expression in the skin also indicates that this gene is useful in wound healing and fibrosis. Expression by neutrophils also indicates that this gene product plays a role in inflammation and the control of immune surveillance (i.e., recognition of viral pathogens). Reverse transcriptase family members are also useful in the detection and treatment of AIDS. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:128 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 286 of SEQ ID NO:128, b is an

integer of 15 to 300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 119

The translation product of this gene shares sequence homology with reverse transcriptase, which is important in the synthesis of a cDNA copy of an RNA molecule, and is a method whereby a retrovirus reverse-transcribes its genome into an inheritable DNA copy.

This gene is expressed primarily in the frontal cortex of brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS and peripheral nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in the frontal cortex, combined with the homology to a reverse transcriptase suggest that this gene is useful in the treatment of cancer and AIDS, particularly of the neural system. The expression in brain indicates that it plays a role in neurodegenerative disorders and in neural degeneration. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of

such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:129 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1261 of SEQ ID NO:129, b is an integer of 15 to 1275, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 120

The translation product of this gene shares homology to a hypothetical protein in *Schizosaccharomyces pombe* (See Genbank Accession No. 2281980).

20

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

IYHLHSWIFFHFKRAFCMCFITMKVIAHCSKLRKCXNAQIS

VFCTTLTASYPT (SEQ ID NO:975), IYHLHSWIFFHFKRAFCMCFITM (SEQ ID NO:976), and/or KVIAHCSKLRKCXNAQISVFCTTLTASYPT (SEQ ID

25

NO:977). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

30

The gene encoding the disclosed cDNA is thought to reside on chromosome 18. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 18.

5 This gene is expressed primarily in adult hypothalamus and to a lesser extent in infant brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders; endocrine function; and vertigo. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS and peripheral nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 The tissue distribution in adult hypothalamus and infant brain indicates that the protein product of this gene is useful for the treatment and diagnosis of neurodegenerative disorders; diagnosis of tumors of a brain or neuronal origin; treatments involving hormonal control of the entire body and of homeostasis, behavioral disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:130 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 458 of SEQ ID NO:130, b is an integer of 15 to 472, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 121

10

The translation product of this gene shares sequence homology with the human IRLB protein which is thought to be important in binding to a c-myc promoter element and thus regulating its transcription (See Genbank Accession No. gi|33969). The gene encoding the disclosed cDNA is thought to reside on chromosome 1.

15 Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: WNLLWYFQRLRLPSILPGLVLASCDGPSXSQAPSPWLTPDPASVQVRLLEDV LTPDPN (SEQ ID NO:978), QRGYREILFLTMAALGKDHVDIVAFDKKYKSAF NKLASSMGKEELRHRAQMP (SEQ ID NO:979), and/or WNLLWYFQRLRLP SILPGLVLAS (SEQ ID NO:980). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 This gene is expressed primarily in brain and breast, and to a lesser extent in a variety of hematopoietic tissues and cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer of the brain and breast; lymphoproliferative disorders; neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, breast, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, breast, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates that the protein product of this gene is useful for the treatment and diagnosis of cancer of the brain, breast, and hematopoietic system. In addition, it is useful for the treatment of neurodegenerative disorders, as well as disorders of the hematopoietic system, including defects in immune competency and inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:131 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1936 of SEQ ID NO:131, b is an integer of 15 to 1950, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 122

5 The translation product of this gene shares sequence homology with an ATP synthase, a key component of the proton channel that is thought to be important in the translocation of protons across the membrane.

This gene is expressed primarily in T-cell lymphoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
10 and for diagnosis of diseases and conditions which include, but are not limited to, T cell lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or
15 lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the
20 disorder.

The tissue distribution in T-cell lymphoma, combined with the homology to an ATP synthase indicates that the protein product of this gene is useful for the treatment of defects in proton transport, homeostasis, and metabolism, as well as the diagnosis and treatment of lymphoma. Because the gene is expressed in cells of
25 lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:132 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:132, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 123**

The gene encoding the disclosed cDNA is thought to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

15 This gene is expressed primarily in a variety of fetal tissues, including fetal liver, lung, and spleen, and to a lesser extent in a variety of blood cells, including eosinophils and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
20 and for diagnosis of diseases and conditions which include, but are not limited to, cancer (abnormal cell proliferation); T cell lymphomas; and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
25 fetus and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. fetal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful for the treatment and diagnosis of conditions involving cell proliferation. Similarly, the fetal tissue expression, as well as the expression in a variety of blood cell lineages, indicates that it may play a role in either cellular proliferation, apoptosis, or cell survival. Thus it may be useful in the management and treatment of a variety of cancers and malignancies. In addition, its expression in blood cells indicates that it may play additional roles in hematopoietic disorders and conditions, and could be useful in treating diseases involving autoimmunity, immune modulation, immune surveillance, and inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:133 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1706 of SEQ ID NO:133, b is an integer of 15 to 1720, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 124

This gene is expressed primarily in placenta, and to a lesser extent in pineal gland and rhabdomyosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, endocrine, and female reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the placenta and endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. placental, endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 372 as residues: Leu-69 to Val-76.

The tissue distribution in placenta indicates that the protein product of this gene is useful for the diagnosis and treatment of developmental disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:134 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 691 of SEQ ID NO:134, b is an integer of 15 to 705, where both a and b correspond to the positions of nucleotide
5 residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 125

10 Contact of cells with supernatant expressing the product of this gene increases the permeability of THP-1 Monocyte cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds a receptor on the surface of the Monocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to,
15 activating monocyte cells.

This gene is expressed primarily in benign prostatic hyperplasia.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of benign prostatic hyperplasia. Similarly, polypeptides and
20 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, cancerous and wounded
25 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in benign prostatic hyperplasia tissue indicates that the
30 protein product of this gene is useful for the treatment and diagnosis of proliferative disorders of the prostate. Furthermore, the biological activity data indicates that the translation product of this gene is useful for the stimulation of certain immune system

cells, such as monocytes, which may be useful for helping the body to defend against infection. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:135 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 309 of SEQ ID NO:135, b is an integer of 15 to 323, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 126

This gene is expressed primarily in Raji cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and T cell autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
25 disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in Raji cells indicates that the protein product of this gene is useful for treatment and diagnosis of inflammation and T cell autoimmune disorders. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases (such as AIDS), and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:136 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 568 of SEQ ID NO:136, b is an integer of 15 to 582, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 127

This gene is expressed primarily in apoptotic T-cells, and to a lesser extent in suppressor T cells and ulcerative colitis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases involving premature apoptosis, and immunological and gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or

lower levels may be routinely detected in certain tissues or cell types (e.g. immune, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 375 as residues: Asp-23 to Gly-29.

The tissue distribution in apoptotic T-cells indicates that the protein product of this gene is useful for the treatment and diagnosis of disorders involving inappropriate levels of apoptosis, especially in immune cell lineages. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases (such as AIDS), and leukemia. Furthermore, expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:137 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1007 of SEQ ID NO:137, b is an integer of 15 to 1021, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 128

The translation product of this gene shares sequence homology with an *C. elegans* coding region C47D12.2 of unknown function (See Genbank Accession No. gnl|PID|e348986).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

5 EDDGFNRSIHEVILKNITWYSERVLTEISLGSLILVVIRTIQYNMTRTRDKYLH
 TNCLAALANMSAQFRSLHQYAAQRIISLFSLLSKKHNVLEQATQSLRGSLS
 NDVPLPDYAQDLNVIEEVIRMMLEINSCLTNSLHHNPNLVYALLYKRDLFEQ
 FRTHPSFQDIMQNIDLVISFFSSRLLQAGS (SEQ ID NO:981),
 10 EDDGFNRSIHEVILKNITWYSERVLTEISLGSLILVV (SEQ ID NO:982),
 RTIQYNMTRTRDKYLHTNCLAALANMSAQFRSLHQYAAQRIISLFSLLSKKH
 N (SEQ ID NO:983),
 SCLTNSLHHNPNLVYALLYKRDLFEQFRTHPSFQDIMQNIDLVISFFSSRLLQA
 GS (SEQ ID NO:984), KKHNVLEQATQSLRGSLSNDVPLPDYAQD (SEQ ID
 15 NO:985), TISNSSFISGYNAKY (SEQ ID NO:986), and/or
 LKVAASWELSCQWNGSWKSLSKASLRC PKTD (SEQ ID NO:987). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 20 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome
 25 18. Accordingly, polynucleotides related to this invention are useful as a marker in
 linkage analysis for chromosome 18.

This gene is expressed primarily in smooth muscle, and to a lesser extent in
 fetal liver/spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 atherosclerosis and other cardiovascular and hepatic disorders. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g. muscle, fetal liver/spleen, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the

10 disorder.

The tissue distribution in smooth muscle indicates that the protein product of this gene is useful for the diagnosis and treatment of circulatory system disorders such as atherosclerosis, hypertension, stroke, aneurysms, embolisms, and thrombosis. In addition, the tissue distribution indicates that the protein product of this gene is useful

15 for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus indicates a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue

20 trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:138 and may have been publicly available prior to conception

25 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1763 of SEQ ID NO:138, b is an

30 integer of 15 to 1777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 129

The translation product of this gene shares sequence homology with a
 5 ribosomal protein which is thought to be important in cellular metabolism, in addition
 to the *C.elegans* protein F40F11.1 which does not have a known function at the
 current time (See Genbank Accession No. gnl|PID|e244552).

In specific embodiments, polypeptides of the invention comprise, or alternatively
 consists of, an amino acid sequence selected from the group:

10 MADIQTERAYQKQPTIFQNKKRVLGETGKEKLPRVTNKNIGLGFKDTPRRL
 LRGTYIDKKCPFTGNVSIRGRILSGVVTQDEDAEDHCHPPRLSALHPQVQPLR
 EAPQEHVCTPVPLLQGRPDR (SEQ ID NO:988),
 MKMQRTIVIRRDYLYIRKYNRFEKRHKNMVHLSVHSPCFRDVQIGDIVTVGEC
 RPLSKTVRFNVLKVTKAAGTKKQFQKF (SEQ ID NO:989),
 15 MADIQTERAYQKQPTIFQNKKRVLGETGK (SEQ ID NO:990),
 KLPRVTNKNIGLGFKDTPRRLLRGTYIDKKCPFTGNVSIRGRILSGVVTQDED
 AEDHC (SEQ ID NO:991),
 HCHPPRLSALHPQVQPLREAPQEHVCTPVPLLQGRPDR (SEQ ID NO:992),
 MKMQRTIVIRRDYLYIRKYNRFEKRHKNMVHLSVHSP (SEQ ID NO:993),
 20 CFRDVQIGDIVTVGECRPLSKTVRFNVLKVTKAAGTKKQFQKF (SEQ ID
 NO:994), PRLLRGTYIDKKCPFTGNVSIRGRILSGVVTQ (SEQ ID NO:995),
 SRGTGVQTCSCGASRSGCTCGCSADSLGG (SEQ ID NO:996), and/or
 QWSSASSSWVTPERIRPRMDTLPVKGHFLSM (SEQ ID NO:997). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 25 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 30 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

5 This gene is expressed primarily in Wilm's tumor, and to a lesser extent in thymus and stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Kidney disorders and cancer, diseases affecting RNA translation. Similarly,
10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Wilm's tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, thymus, cancerous and
15 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
20 NO: 377 as residues: Arg-15 to Gly-22.

The tissue distribution in Wilm's tumor, combined with the homology to a ribosomal protein indicates that the protein product of this gene is useful for diseases affecting RNA translation, in addition to proliferative disorders. Furthermore, given the tissue distribution, the translation product of this gene may be useful in treating
25 and/or detecting Wilm's tumor or tumors of other tissues mentioned previously. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
30 related to SEQ ID NO:139 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 629 of SEQ ID NO:139, b is an integer of 15 to 643, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 130

The translation product of this gene shares sequence homology with a yeast DNA helicase, which is thought to be important in global transcriptional regulation (See Genbank Accession No. gnl|PID|e243594).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

IFYDSDWNPTVDQQAMDRAHRLGQTKQVTYRLICKGTIEERILQRAKEKSEI
 QRMVISG (SEQ ID NO:998),
 TRMIDLLEEYMVYRKHTYXRLDGSSKISERRDMVADFQNRNDIFVLLSTRA
 GGLGINLTAXDTVHF (SEQ ID NO:999),
 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTYR (SEQ ID NO:1000),
 VYRLICKGTIEERILQRAKEKSEIQRMVISG (SEQ ID NO:1001),
 TRMIDLLEEYMVYRKHTYXRLDGSSKISERRDM (SEQ ID NO:1002),
 RRDMVADFQNRNDIFVLLSTRAGGLGINLTAXDTVHF (SEQ ID NO:1003),
 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTYRLICKG (SEQ ID NO:1004),
 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTYRLICKG (SEQ ID NO:1005),
 RLICKGTIEERILQRAKEKSEIQRMVISG (SEQ ID NO:1006), and/or
 GTRMIDLLEEYMVYRKHTYXRLDGSSKISERRDMVADFQNRNDIFVLLSTR
 AGGLGINLTAXDTVHFL (SEQ ID NO:1007). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are

also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in amygdala.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and disorders of the brain and the endocrine system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 378 as residues: Lys-24 to Tyr-34.

The tissue distribution in amygdala, combined with the homology to a DNA helicase indicates that the protein product of this gene is useful for diseases affecting RNA transcription, particularly developmental disorders and healing wounds, since the later are thought to approximate developmental transcriptional regulation. The amygdala processes sensory information and relays this to other areas of the brain including the endocrine and autonomic domains of the hypothalamus and the brain stem. Therefore, the translation product of this gene is also useful for the detection and/or treatment of disorders of the endocrine and/or neural systems. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:140 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1206 of SEQ ID NO:140, b is an integer of 15 to 1220, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 131

10

This gene is expressed primarily in prostate, and to a lesser extent in amygdala and pancreatic tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate enlargement and gastrointestinal disorders, particularly of the pancreas and gall bladder. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate indicates that the protein product of this gene is useful for the treatment and diagnosis of prostate or reproductive diseases, including benign prostatic hyperplasia and prostate cancer. In addition, the tissue distribution in tumors of the pancreas indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tissues where expression has been indicated. Protein, as well as, antibodies directed against

the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:141 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 707 of SEQ ID NO:141, b is an integer of 15 to 721, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 132**

The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

20 This gene is expressed primarily in adult lung, and to a lesser extent in the hypothalamus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary diseases and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adult lung indicates that the protein product of this gene is useful for the diagnosis and treatment of pulmonary and respiratory disorders such as emphysema, pneumonia, and pulmonary edema and emboli. In addition, the tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:142 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1454 of SEQ ID NO:142, b is an integer of 15 to 1468, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 133

This gene is expressed primarily in human liver.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

cirrhosis of the liver and other hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human liver indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:143 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 286 of SEQ ID NO:143, b is an integer of 15 to 300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 134

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

5 This gene is expressed primarily in fetal kidney, and to a lesser extent in fetal liver and spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, development and regeneration of liver and kidney and immunological disorders.

10 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and excretory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney,

15 liver, spleen, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 382 as residues: Pro-70 to Arg-77, Tyr-102 to Thr-107.

The tissue distribution in fetal kidney indicates that the protein product of this gene is useful for the diagnosis and treatment of diseases of the kidney and liver, such as cirrhosis, kidney failure, kidney stones, and liver failure, hepatoblastoma, jaundice,

25 hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility

30 as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:144 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2229 of SEQ ID NO:144, b is an integer of 15 to 2243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 135

This gene is expressed primarily in brain, bone marrow, and to a lesser extent in placenta, T cell, testis and neutrophils.

15

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative and immunological diseases and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
20 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine,
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 383 as residues: Met-1 to His-6.

The tissue distribution in brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral

disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in T cells and neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:145 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1068 of SEQ ID NO:145, b is an integer of 15 to 1082, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 136

25

The translation product of this gene is homologous to the human WD repeat protein HAN11, which is thought to function in signal transduction pathways. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MSLHGKRKEIYKYEAPWTVYAMNWSVRPDKRFRLLALGSFVEEYNNKVQLV
GLDEESSEFICRNTFDHPYPTTKLMWIPDTKGVYPDLLATSGDYLRVWRVGE
TETRLECLLNNNKNSDFCAPLTSFDWNEVDPYLLGTSSIDTTCTIWGLETGQV

30

LGRVNLVSGHVKTQLIAHDKEYVDIAFSRAGGGRDMFASVGADGSVRMFDL
 RHLEHSTIYEDPQHHP LLRLCWNKQDPNYLATMAMDGMEVVILDVRVPAH
 LXPGTTIEHVSMALLGPHIHPATSALQRM TTRLSSGTSSKCPEPLRTLSWPTQL
 XGEINNVQWASTQPELSPSATT TAWRYSECSVGGAVPTRQGLLYFLPLPHPQS
 5 (SEQ ID NO:1008),
 MSLHGKRKEIYKYEAPWTVYAMNWSVRPDKRFR LALGSFVEEYNNKVQLV
 GLDEESSEFICRNTFDHPYPTTKLMWIPDTKGVYPDLLATSGDYLRVWRVGE
 TETRLECLLNNNKN SDFCAPLTSFDWNEVDPYLL (SEQ ID NO:1009),
 SFDWNEVDPYLLGTSSIDTTCTIWGLETGQVLGRVNLVSGHVKTQLIAHDKE
 10 VYDIAFSRAGGGRDMFASVGADGSVRMFDLRHLEHSTIYEDPQHHP LLRLC
 WNKQDPNYLATMAMDGMEVVILDVRVPAHLXPGTTI (SEQ ID NO:1010),
 and/or VGADGSVRMFDLRHLEHSTIYEDPQHHP LLRLCWNKQD
 PNYLATMAMDGMEVVILDVRVPAHLXPGTTIEHVSMALLGPHIHPATSALQR
 M TTRLSSGTSSKCPEPLRTLSWPTQLXGEINNVQWASTQPELSPSATT TAWRY
 15 SECSVGGAVPTRQGLLYFLPLPHPQS (SEQ ID NO:1011). Moreover, fragments
 and variants of these polypeptides (such as, for example, fragments as described
 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%
 identical to these polypeptides and polypeptides encoded by the polynucleotide which
 hybridizes, under stringent conditions, to the polynucleotide encoding these
 20 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome
 17. Accordingly, polynucleotides related to this invention are useful as a marker in
 25 linkage analysis for chromosome 17.

This gene is expressed primarily in placenta, embryo, T cell and fetal lung,
 and to a lesser extent in endothelial, tonsil and bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 30 and for diagnosis of diseases and conditions which include, but are not limited to,
 immunological and developmental diseases in addition to cancers. Similarly,
 polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and
5 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
10 NO: 384 as residues: Gly-19 to Gln-28, Pro-36 to Phe-42.

The tissue distribution in tumors of colon, ovary, and breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Because the gene is expressed in cells of lymphoid origin, the natural gene product
15 may be involved in immune functions. Therefore it may also be used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:146 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4299 of SEQ ID NO:146, b is an integer of 15 to 4313, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 137

This gene is expressed primarily in TNF and INF induced epithelial cells, T cells and kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory conditions particularly inflammatory reactions in the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 385 as residues: Thr-67 to Gly-72, Gln-132 to Ala-145, Arg-150 to Pro-157.

The tissue distribution in TNF and INF induced epithelial cells indicates that the protein products of this gene are useful for treating the damage caused by inflammation of the kidney. Furthermore, the tissue distribution in kidney indicates that this gene or gene product is useful in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:147 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 1169 of SEQ ID NO:147, b is an integer of 15 to 1183, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.

10. **FEATURES OF PROTEIN ENCODED BY GENE NO: 138**

The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1. (See Genbank Accession No. D63485).

15 This gene is expressed primarily in breast cancer and colon cancer, and to a lesser extent in thymus and fetal spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
20 cancers, especially of the breast and colon tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain
25 tissues or cell types (e.g. breast, colon, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in tumors of colon and breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as

well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:148 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:148, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 139

The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

20 This gene is expressed primarily in CD34 positive cells, and to lesser extent in activated T-cells and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune related diseases and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34 positive cells, T-cells and neutrophils indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic disorders and immune related diseases, such as anemia, leukemia, inflammation, infection, allergy, immunodeficiency disorders, arthritis, asthma, immune deficiency diseases such as AIDS. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells and neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:149 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1391 of SEQ ID NO:149, b is an integer of 15 to 1405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 140

This gene was recently published by another group, who called the gene KIAA0313 gene. (See Genbank Accession No. d1021609.)

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- LYATATVISSPSTEXLSQDQGDRA SLDAADSGRGSWTSCSSGSHDNIQTIQHQR
 RSWETLFPFGHTHFDYSGDPAGLWASSSHMDQIMFSDHSTKYNRQNQSRESLE
 QAQSRASWASSTGYWGEDSEGDGTGIKRRGGKDV SIEAESSSLTSVTTEETKP
 10 VPMPAHIAVASSTTKGLIARKEGRYREPPPTPPGYIGIPITDFPEGHSH PARKPP
 DYNVALQR SRMVARSSDTAGPSSVQQPHGHPTSSRPVNKPQWHKXNESDPR
 LAPYQSQGFSTEDEDEQVSAV (SEQ ID NO:1012),
 HMDQIMFSDHSTKYNRQNQSRESLEQAQSRASWASSTGYWGE (SEQ ID
 NO:1013),
 15 SVTTEETKPVMPAHIAVASSTTKGLIARKEGRYREPPPTPPGYIGIPITD (SEQ
 ID NO:1014), and/or
 VALQR SRMVARSSDTAGPSSVQQPHGHPTSSRPVNKPQWHKXNESDPR LAP
 YQSQGF (SEQ ID NO:1015). Moreover, fragments and variants of these
 polypeptides (such as, for example, fragments as described herein, polypeptides at
 20 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent
 conditions, to the polynucleotide encoding these polypeptides) are encompassed by
 the invention. Antibodies that bind polypeptides of the invention are also
 encompassed by the invention. Polynucleotides encoding these polypeptides are also
 25 encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4. (See Genbank Accession No. AB002311).

- 30 This gene is expressed primarily in ovarian cancer, tumors of the Testis, brain, and colon.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, ovarian, testicle, brain and colon cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male and female reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, testis, colon, ovary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of colon, ovary, testis, and brain origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:150 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2876 of SEQ ID NO:150, b is an integer of 15 to 2890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 141

The gene encoding the disclosed cDNA is thought to reside on chromosome 18. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 18.

This gene is expressed primarily in spleen and colon cancer.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, colon cancer and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for
10 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal tract and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. spleen, colon, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid
15 and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in colon tumors indicates that the protein product of this gene is useful for the diagnosis and intervention of such tumors, in addition to
20 other tissues and cell types where expression has been indicated. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be
25 also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and
30 graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In

addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the
 5 above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
 10 related to SEQ ID NO:151 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 15 formula of a-b, where a is any integer between 1 to 2385 of SEQ ID NO:151, b is an integer of 15 to 2399, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.

20 **FEATURES OF PROTEIN ENCODED BY GENE NO: 142**

The translation product of this gene is homologous to a T cell translocation protein, a putative zinc finger factor (See Genbank Accession No. 340454), as well as to the G-protein coupled receptor TM5 consensus polypeptide (See Genbank
 25 Accession No. R50734).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
 CLLFV FVSLGM RCLFW TIVYN VLYLKH KCNTV LLCYHL CSI (SEQ ID
 NO:1016), and/or
 30 ACSKLIP AFEMVM RAKDN VYHLDC FACQL CNQRX CVGDK FFLKNNXXLCQ
 TDYEEGLMKEGYAPXVR (SEQ ID NO:1017). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are
5 also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal brain, and to a lesser extent in frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, including brain cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
15 the above tissues or cells, particularly of the Central Nervous System, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's
25 Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse
30 formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:152 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 788 of SEQ ID NO:152, b is an integer of 15 to 802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 143

The translation product of this gene has significant homology to the Fas ligand, which is a cysteine-rich type II transmembrane protein/tumor necrosis factor receptor homolog. Mutations within this protein have been shown to result in generalized lymphoproliferative diseases leading to the development of lymphadenopathy and autoimmune disease (See Medline Article No. 94185175).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
SALSEPGAPDRRRPCPESVPRRPDDEQWPPPTALCLDVAPLPPSS (SEQ ID NO:1018). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention. (See Genbank Accession No. 473565).

This gene is expressed primarily in osteoblasts, lung, and brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteoblast-related, pulmonary, neurological, and immunological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, brain, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 391 as residues: Trp-33 to Thr-40, Lys-45 to Ile-63.

The tissue distribution in osteoblasts, lung, and brain, combined with its homology to the Fas ligand, indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Because the Fas ligand gene is known to be expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including asthma, immune deficiency diseases such as AIDS and leukemia, and various autoimmune disorders including lupus and arthritis. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:153 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 5 formula of a-b, where a is any integer between 1 to 447 of SEQ ID NO:153, b is an integer of 15 to 461, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.

10 FEATURES OF PROTEIN ENCODED BY GENE NO: 144

This gene shares sequence homology with a 21.5 KD transmembrane protein in the SEC15-SAP4 intergenic region of yeast. (See Genbank Accession No. 1723971.)

- 15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: PVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQIPMNLFI (SEQ ID NO:1019),
- AHASESGERWWACCGVRFGRLRSIEAIGRSCCHDGPGLVANRGRFRKWAIEL
- 20 SGPGGGSRRSDRGSGQGDSLVPVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQIPMNLFIMYMAGNTISIFPTMMVCMMAWRPIQALMAISATFKMLES
- SSQKFLQGLVYLIGNLMGLALAVYKCQSMGLLPHTASDWLAFIEPPERMEFS
- GGGLLL (SEQ ID NO:1020), PVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQIPMNLFI (SEQ ID NO:1022), and/or
- 25 ATFKMLESSQKFLQGLVYLIGNLMGLALAVYKCQSMGLLPHTASD (SEQ ID NO:1021). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
- 30 encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in osteoclastoma, hemangiopericytoma, liver, lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteoclastoma, hemangiopericytoma, liver and lung tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the above tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lung and liver systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of tumors of the osteoclastoma, hemangiopericytoma, liver and lung, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:154 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2374 of SEQ ID NO:154, b is an integer of 15 to 2388, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 145

5 The translation product of this gene shares homology with the glucagon-69 gene which may indicate this gene plays a role in regulating metabolism. (See Genbank Accession No. A60318)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
PTTKLDIMEKKKKHIQIRFPSFYHKLVDSGRMRSKRETRREDSDTKHNL (SEQ
10 ID NO:1023), FLWKSLLRLRYFKMRQH (SEQ ID NO:1024), and/or
YHYLLSSFLSYSSSSQNLVPYGRKMGTLFECVFFFP (SEQ ID NO:1025).
Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
15 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain, kidney, colon, and testis.
20 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain, kidney, colon, and testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for
25 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, neurological, circulatory, and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, kidney, colon, testis, cancerous and wounded tissues) or bodily fluids (e.g.,
30 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain, kidney, colon, and testis origins, indicates that the protein product of this gene is useful for the diagnosis and intervention of tumors of these tissues. The protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. The tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:155 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 5 formula of a-b, where a is any integer between 1 to 628 of SEQ ID NO:155, b is an integer of 15 to 642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.

10 FEATURES OF PROTEIN ENCODED BY GENE NO: 146

The translation product of this gene shares sequence homology with goliath protein, which is a Drosophila protein thought to be important in the regulation of gene expression during development. Protein may serve as a transcription factor.

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

TEHILAVMITELRGKDILSYLEKNISVQMTIAVGTRMPPKNFSRGS�VFVSISFI
 VLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKKGDKE
 TDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCPMCKLNI

20 LKALGIV (SEQ ID NO:1026),

MTHPGTEHILAVMITELRGKDILSYLEKNISVQMTIAVGTRMPPKNFSRGS�VF
 VSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKK
 GDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCPMC
 KLNILKALGIVPNLPCTDNVAFD MERLTRTQAVNRRSALGDLAGDNSLGLPE

25 LRTSGISPLPQDGELTPRTGEINIAVTKEWFILASFGLLSALTLCYMIIRATASLN
 ANEVEWF (SEQ ID NO:1027),

TEHILAVMITELRGKDILSYLEKNISVQMTIAVGTRMPPKNFSRGS�VFVSISFI
 VLMISSAWLIFYF (SEQ ID NO:1028),

SISFIVLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKKG
 30 DKE (SEQ ID NO:1029),

VKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTC
 PMCKLNILKALGIV (SEQ ID NO:1030),

MTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTI
 AVGTRMPPKNFSRGS LVFVSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRRRL
 GDAAKKAISKLTTRT (SEQ ID NO:1031),
 AAKKAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHK
 5 SCVDPWLSEHCTCPMCKLNILKALGIVPNLPC (SEQ ID NO:1032),
 TQAVNRRSALGDLAGDNSLGLLEPLRTSGISPLPQDGELTPRTGEINIAVTKEWF
 IASFGLLSALTLCYMIIRATASLNANEVEWF (SEQ ID NO:1033),
 PLHGVADHLGCDPQTRFFVPPNIKQWIALLRGNCTFKEKISRAAFHNAVAV
 VIYNNKSKEEPVTMTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTIAVGTR
 10 MPPKNFSRGS LVFVSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRRRLGDAAK
 KAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCV
 DPWLSEHCTCPMCKLNILKALGIVPNLPCTDNVAFDMERLRTTQAVNRRSAL
 GDLAGDNSLGLLEPLRTSGISPLPQDGELTPRTGEINIAVTKEWF IASFGLLSAL
 TLCYMIIRATASLNANEVEWF (SEQ ID NO:1034), and/or
 15 HGVADHLGCDPQTRFFVPPNIKQWIALLRGNCTFKEKISRAAFHNAVAVVI
 YNNKSKEE (SEQ ID NO:1035). Moreover, fragments and variants of these
 polypeptides (such as, for example, fragments as described herein, polypeptides at
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent
 20 conditions, to the polynucleotide encoding these polypeptides) are encompassed by
 the invention. Antibodies that bind polypeptides of the invention are also
 encompassed by the invention. Polynucleotides encoding these polypeptides are also
 encompassed by the invention. (See Genbank Accession No. 157535).

When tested against Jurkat cell lines, supernatants removed from cells
 25 containing this gene activated the GAS assay. Thus, it is likely that this gene
 activates T-cells through the Jak-STAT signal transduction pathway. The gamma
 activating sequence (GAS) is a promoter element found upstream of many genes
 which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large,
 signal transduction pathway involved in the differentiation and proliferation of cells.
 30 Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS
 element, can be used to indicate proteins involved in the proliferation and
 differentiation of cells.

This gene is expressed primarily in macrophage, breast, kidney and to a lesser extent in synovium, hypothalamus and rhabdomyosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, schizophrenia and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and neural system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, kidney, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in macrophage, hypothalamus, and kidney, combined with the homology to a zinc finger protein indicates that the protein product of this gene is useful for the treatment of schizophrenia, kidney disease and other cancers. Furthermore, the tissue distribution in macrophage, breast, and kidney origins indicates that the protein product of this gene is useful for the diagnosis and intervention of tumors within these tissues, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:156 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:156, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide
 5 residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 147

10 The translation product of this gene shares sequence homology with HNP36 protein, an equilibrative nucleoside transporter, which is thought to be important in gene transcription as well as serving as an important component of the nucleoside transport apparatus (See Genbank Accession No. 1845345).

In specific embodiments, polypeptides of the invention comprise, or
 15 alternatively consists of, an amino acid sequence selected from the group:

MSGQGLAGFFASVAMICAIASGSELSESAFGYFITACAVIILTII CYLGLP
 RLEFYRYYQQLKLEGPGEQETKLDLISKGEEPRAGKEESGVSVSNSQPTNESH
 SIKAILKNISVLAFSVCFTITIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLTF
 NIFDWLGRSLTAVFMWPGKDSRWLPSWXLARLVFVPLLLLCNIKPRRYLTVV
 20 FEHDAWFIFFMAAFASNGYLASLCMCFGPKKVKPABAEAEPSWPSSCVW
 VWHWGLFSPSCSGQLCDKGWTEGLPASLPVCLLPLPSARGDPEWSGGFFF (SEQ
 ID NO:1036),

MSGQGLAGFFASVAMICAIASGSELSESAFGYFITACAVIILTII CYLGLPRLEF
 YRYYQQLKLEGPGEQETKLDLISKGEEPRAGKEESGVSVSNSQPTNESH
 25 (SEQ ID NO:1037),

SGVSVSNSQPTNESH SIKAILKNISVLAFSVCFTITIGMFPAVTVEVKSSIAGS
 STWERYFIPVSCFLTFNIFDWLGRS (SEQ ID NO:1038),

TIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLTFNIFDWLGRSLTAVFMWPG
 KDSRWLPSWXLARLVFVPLLLLCNIKPRRYLTVVFEHDA (SEQ ID NO:1039),

30 and/or

FGPKKVKPABAEAEPSWPSSCVWVWHWGLFSPSCSGQLCDKGWTEGLPAS
 LPVCLLPLPSARGDPEWSGGFFF (SEQ ID NO:1040). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments. The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in eosinophils and aortic endothelium, and to a lesser extent in umbilical vein endothelial cell and thymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hemopoietic disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. circulatory, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution eosinophils and aortic endothelium, combined with the homology to the HNP36 protein indicates that the protein product of this gene is useful for the treatment of blood neoplasias and other hemopoietic disease. Furthermore, elevated expression of this gene product by endothelial cells indicates that it may play vital roles in the regulation of endothelial cell function; secretion; proliferation; or angiogenesis. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:157 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:157, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 148

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

20 This gene is expressed primarily in breast cancer cell lines, thymus stromal cells, and ovary.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine and female reproductive system diseases including breast cancer.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. thymus, ovary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having

such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast cancer cells and ovary indicates that the protein product of this gene is useful for the diagnosis and treatment of endocrine disorders. In addition, the tissue distribution in tumors of thymus, ovary, and breast origins indicates that the protein product of this gene is useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:158 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1611 of SEQ ID NO:158, b is an integer of 15 to 1625, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 149

The translation product of this gene has homology to pmt1 and pmt 2, two conserved Schizosaccharomyces pombe genes.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: DDDGFEIVPIEDPAKHRILDPEGLALGAVIASSKKAKRDLIDNSFNRYTFNEDE
GELPEWVFVQEEKQHRIRQLPVGKKEVEHYRKRWREINARPIXXXXXXXXXXXX
XXXXXXXXLEQTRKKA EAVVNTVDIXRTRES (SEQ ID NO:1041), DDDG
FEIVPIEDPAKHRILDPEGLALGAVIASSKKAKRDLIDNSFNRYTF (SEQ ID

NO:1042),

and/or

KRWREINARPIXXXXXXXXXXXXXXXXXXXXLEQTRKKAEAVVNTVDIXRTRES

(SEQ ID NO:1043). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. e1216734).

This gene is expressed primarily in retina and ovary, and to a lesser extent in breast cancer cells, epididymus and osteosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neuronal growth disorders, cancer and reproductive system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. retina, ovary, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 397 as residues: Met-1 to Gly-7.

The tissue distribution in ovary, breast cancer cells, and epididymus indicates that the protein product of this gene is useful for the diagnosis or treatment of reproductive system diseases and cancers, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the

protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:159 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1673 of SEQ ID NO:159, b is an integer of 15 to 1687, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 150

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MIKDKGRARTALTSSQPAHLCPENPLLHLKAAVKEKKRNKKKKKTIGSPKRIQS
 20 PLNNKLLNSPAKTLPGACGSPQKLIDGFLKHEGPPAEKPLEELSASTSGVPGLS
 SLQSDPAGCVRPPAPNLAGAVEFNDVKTLLEWITTISDPMEEDILQVVKYCT
 DLIEEKDLEKLDLVIKYMKRLMQQSVESVWNMAFDNFILDNVQVVLQQTYGS
 TLKVT (SEQ ID NO:1044),
 MIKDKGRARTALTSSQPAHLCPENPLLHLKAAVKEKKRNKKKKKTIGSPKRIQ
 25 (SEQ ID NO:1045),
 KRIQSPLNNKLLNSPAKTLPGACGSPQKLIDGFLKHEGPPAEKPLEELSASTSG
 VPGLSSLQSDPAGCVRPPAPNLAGAVEFNDVKTLLEWITTISDPM (SEQ ID
 NO:1046),
 TISDPMEEDILQVVKYCTDLIEEKDLEKLDLVIKYMKRLMQQSVESVWNMAF
 30 DFILDNVQVVLQQTYGSTLKVT (SEQ ID NO:1047),
 VCCKTTWTLSRIKSNAIFQTDSTDCCISLFMYFITRSSFSKSFSSIRSVQYFTTW
 RMSSSIGSEIVVIHSLSKVFTSLNSTAPARLGAGGLTQPAGSDCKLERPGTPEV

EAESSSRGFSAGGPSCFRNPSINFWGLPQAPGRVFAGLLSSLLFKGL (SEQ ID NO:1048), WTLSRIKSNAIFQTDSTDCISLFM (SEQ ID NO:1049), FTTWRMSSSIGSEIVVIHSLSKVFTSLNSTAPARLGA (SEQ ID NO:1050), and/or GGPSFCFRNPSINFWGLPQAPGRVFAGLL (SEQ ID NO:1051). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in 12 week embryo, and to a lesser extent, in hemangiopericytoma and frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental or neural disorders, particularly hemangiopericytoma, and other proliferative conditions, including cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural system and developing systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 398 as residues: Leu-4 to Lys-11.

The tissue distribution in embryonic and neural tissues indicates that the protein product of this gene is useful for the treatment of growth disorders, hemangiopericytoma and other soft tissue tumors. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:160 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1828 of SEQ ID NO:160, b is an integer of 15 to 1842, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 151

The translation product of this gene has been found to have homology to a
5 human DNA mismatch repair protein PMS3 (See Genbank Accession No. R95250).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: FCHDCKFPEASPAMNCEP (SEQ ID NO:1052), FCHDCKFPEASPAMNCEP (SEQ ID NO:1053), and/or HEPYAVLVI (SEQ ID NO:1054). Moreover, fragments
10 and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
15 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
20 and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as lymphoma, immunodeficiency diseases, and cancers resulting from genetic instability. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
25 the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
30 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 399 as residues: Met-1 to Lys-6.

The tissue distribution in neutrophils, combined with the sequence homology to a human mismatch DNA repair enzyme indicates that the protein product of this gene is useful for diagnosis of Hodgkin's lymphoma, since the elevated expression and secretion by the tumor mass may be indicative of tumors of this type. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, its homology to a known DNA repair protein would suggest the gene may be useful in establishing cancer predisposition and prevention or be of use in gene therapy applications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:161 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 756 of SEQ ID NO:161, b is an integer of 15 to 770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 152

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
PQPSNFPTTVRNLPYSGAGAQPSPSNC (SEQ ID NO:1055). Moreover, fragments

and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are
5 encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as infectious diseases and lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell
15 type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an
20 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment of inflammation and infectious diseases. Expression
25 of this gene product in neutrophils indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the
30 gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such

as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:162 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 505 of SEQ ID NO:162, b is an integer of 15 to 519, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 153

25

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSA
HSLPLHPLSASCSAPACHASDTHLLYPSTRALCPSIFAWLVAPHSVFRTNAPGP
30 TPSSQSSPVFPVFPVSFMAIVCXLVCC (SEQ ID NO:1056),
MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSA
HSLPLHPLSASCSAPACHA (SEQ ID NO:1057),

FAWL VAPHSVFRTNAPGPTPSSQSSPVFPVFPVSFMA LIVCXLVCC (SEQ ID NO:1058),
MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSA
HSLPLHPLSASCSAPACHASDTHLLYPSTRALCPSIFAWLVAPHSVFRTNAPGP
5 TPSSQSSPVFPVFPVSFMA LIVCXLVCC (SEQ ID NO:1059),
LVNWILKLHCLNLFSGFPLYLEKNATSSAGTHPLTAFPSTLSLPHALPLPAMPP
ILTFCTPAPVPSAPRSLPGWLLLTQCSGQMLLALPHLASLARSSLSL FHSWLL
LFVXLCAVDF (SEQ ID NO:1060), NLFSGFPLYLEKNATSSAGTHPL (SEQ ID NO:1061), and/or PHLASLARSSLSL FHSWLL (SEQ ID NO:1062). Moreover,
10 fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
15 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
20 and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as inflammation and infectious diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
25 immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 401 as residues: Ser-11 to Pro-17.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment of infectious diseases and inflammation. Moreover, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:163 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 739 of SEQ ID NO:163, b is an

integer of 15 to 753, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 154

This gene is primarily expressed in ovary, uterus, adipose tissue, brain, and the liver.

Polynucleotides and polypeptides of the invention are useful as reagents for
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, neural, hepatic, and metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
15 disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., ovary, uterus, adipose tissue, brain, liver, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
20 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 402 as residues: Asn-56 to Gly-67.

25 The tissue distribution of this gene product in ovary and uterus indicates that the protein product of this gene is useful for diagnostic or therapeutic uses in the treatment of the female reproductive system, obesity, and liver disorders, particularly cancer in the above tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed
30 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:164 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1879 of SEQ ID NO:164, b is an integer of 15 to 1893, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 155

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in
15 linkage analysis for chromosome 3.

This gene is expressed in multiple tissues including brain, aortic endothelial cells, smooth muscle, pituitary, testis, melanocytes, spleen, neutrophils, and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
20 and for diagnosis of diseases and conditions which include, but are not limited to, immunological or vascular disorders, including immunodeficiencies, cancers of the brain and the female reproductive system, as well as cardiovascular disorders, such as atherosclerosis and stroke. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
25 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, vascular, endothelial, neural, hematopoietic, reproductive, integumentary, placental, endocrine, and cancerous and wounded
30 tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having

such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neural tissue indicates that the protein product of this gene is useful in the treatment/detection of disorders in the nervous system, including schizophrenia, neurodegeneration, neoplasia, brain cancer as well as vascular and female reproductive disorders, including cancer within the above tissues. Moreover, the protein product of this gene may also be useful in the treatment and/or detection of other vascular disorders which include, but are not limited to, aneurysms, emboli, thrombosis, atherosclerosis, microvascular disease, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:165 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2139 of SEQ ID NO:165, b is an integer of 15 to 2153, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 156

25

The translation product of this gene shares sequence homology with the human gene encoding cytochrome b561 (See Genbank Accession No. P10897). Cytochrome b561 is a transmembrane electron transport protein that is specific to a subset of secretory vesicles containing catecholamines and amidated peptides. This protein is thought to supply reducing equivalents to the intravesicular enzymes dopamine-beta-hydroxylase and alpha-peptide amidase.

30

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MAMEGYWRFLALLGSALLVGFLSVIFALVWVLHYREGLGWDGSALEFNWH
 PVLMTGTFVFIQGLAIVYRLPWTWKCSKLLMKSIHAGLNAVAAILAISVVAV
 5 FENHNVNNLANMYSLSWVGLIAVICYLLQLLSGFSVFLPWAPLSLRAFLMP
 IHVYSGIVIFGTVIATALMGLTEKLIFSLRDPAYSTFPPEGVFVNTLGLLLLVFG
 ALIFWIVTRPQWKRPKEPNSTILHPNGGTEQGARGSMPAYSGNNMDKSDSEL
 NSEVAARKRNLAALDEAGQRSTM (SEQ ID NO:1063),

AHASAHASGGAEYGAL (SEQ ID NO:1064),

10 QYSQYVQSAQLGWTDSCHMLFVTASFRFFSLASMGSAFSPSISHAHTCLFW
 NCHLWNDCNSTYGIDRETDFFPERSCIQYIPARRCFRKYAWPSDPGVRGPHF
 LDHQAMETS (SEQ ID NO:1065), ASMG

AFSPSISHAHTCLFWNCHLWNDCNSTYG (SEQ ID NO:1066),

FVHVVARVGWHGTSCSLFSASIWMKNGRIWLLRTFPLRSGDYPKNEGPEHQ

15 DQKAKRIYENTFWRECTVCRISQGNQFLCQSHKCCCNHCSKDDNSRINMY
 GHEKCSERKRSPWKQKD (SEQ ID NO:1067), and/or

ASIWMKNGRIWLLRTFPLRSGDYPKNEGPEHQ (SEQ ID NO:1068). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

20 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

25 The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in anergic T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, and metabolic related diseases. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not

10 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 404 as residues: Pro-222 to Asn-231, Asn-238 to Gly-247, Ala-251 to Leu-264, Ala-280 to Thr-285.

The tissue distribution in anergic T-cells indicates that the protein product or

15 mRNA of this gene is useful for the treatment or diagnosis of immune system and metabolic diseases or conditions including Tay-Sachs disease, phenylketonuria, galactosemia, various porphyrias, and Hurler's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:166 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:166, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 157

The translation product of this gene shares sequence homology with collagen which is important in mammalian development. This gene also shows sequence homology with bcl-2 and the HNK-1 sulfotransferase of *Rattus norvegicus* which is thought to be involved in carbohydrate biosynthesis. (See Genbank Accession No. P80988 and AF022729, respectively.) When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
PGRAGPSPGLSLQLPAEPGHPAGNLAPLTSRPQPLCRIPAVPG (SEQ ID NO:1069). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in HL-60 tissue culture cells, and to a lesser extent, in liver, breast, and uterus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological diseases, hereditary disorders involving the MHC class of immune molecules, as well as developmental disorders and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the immune and reproductive system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, hepatic, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 405 as residues: Ser-39 to Gly-46, Leu-49 to Ala-62.

15 The tissue distribution in reproductive, and immune tissues, combined with the homology to collagen and the detected GAS biological activity indicates that the protein product of this gene is useful for diagnosis and treatment of hereditary MHC disorders and particularly autoimmune disorders including rheumatoid arthritis, lupus, scleroderma, and dermatomyositis, as well as many reproductive disorders, including cancer of the uterus, and breast tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:167 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 868 of SEQ ID NO:167, b is an integer of 15 to 882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 158

This gene is expressed primarily in the amygdala region of the brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, a variety of brain disorders, particularly those effecting mood and personality, in addition to neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in the amygdala indicates that the protein product of this gene is useful for the treatment and/or diagnosis of a variety of brain disorders, particularly bi-polar disorder, uni-polar depression, and dementia. Moreover, The tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role

in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:168 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1194 of SEQ ID NO:168, b is an integer of 15 to 1208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 159

This gene is expressed in a variety of tissues and cell types including brain,
20 smooth muscle, kidney, salivary gland, and T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, renal, vascular, metabolic, or immune disorders, particularly cancers.
25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous, urinary, salivary, digestive, and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain
30 tissues or cell types (e.g., neural, renal, vascular, metabolic, immune cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 407 as residues: Asp-43 to Asp-60.

5 The tissue distribution in brain, smooth muscle, and T-cells indicates that the protein product of this gene is useful for diagnosis of various neurological, and cardiovascular disorders, but not limited to cancer within the above tissues. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene
10 product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:169 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
20 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1244 of SEQ ID NO:169, b is an integer of 15 to 1258, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 160

30 The translation product of this gene shares sequence homology with collagen, which is thought to be important in cellular interactions, extracellular matrix formation, and has been found to be an identifying determinant in autoimmune disorders. Moreover, this gene shows sequence homology with the yeast protein,

- Sls1p, an endoplasmic reticulum component involved in the protein translocation process in the Yeast *Yarrowia lipolytica*. (See Genbank Accession No. 1052828; see also J. Biol. Chem. 271, 11668-11675 (1996).) In *Mus musculus*, this same region shows sequence homology with the heavy chain of kinesin. (See Genbank Accession No. 2062607.) Recently, suppression of the heavy chain of kinesin was shown to inhibit insulin secretion from primary cultures of mouse beta-cells. (See Endocrinology 138 (5), 1979-1987 (1997).) Moreover, kinesin was found associated with drug resistance and cell immortalization. (See Genbank Accession No. 468355.) Thus, it is likely that this gene also acts as a genetic suppressor element.
- 10 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: ARGRRRGRLELWELCLPLGCRRRRSLTMAPQSLPSSRMAPLG (SEQ ID NO:1070),
- NGQASTAKMSSCLRSPPTLAPLSLTSGIPVQSWCGASSQLLQQAVDRAQQLL
- 15 EVALVLTILQLQAGQHLVLSLQAGQCPAELGVLTVAVPAGGQEDAQCLQHL LTGIMLGQRQEVGRDLAPALFPQAWQEVYLAILLQLLWGHLLGQLSLLLGEH LLRDQVVEQCDHAHGEHLRALLHQGPQDLQPPELQELPLGIGEVAQQGAQ CKQDLLLCSERLLRGQDDQQLQGSPFDGLHLDLGVAGKGSAQHKSILLHE GLCAVQPIDHHLKTTKGKQVLRIVHLMDFKIKERSNLLFQTGAGTIELVDQP
- 20 YHDLHVSLNDNIQLIKVFLQFLNGAEEPLYLSLPCLVFL (SEQ ID NO:1071), QHLVLSLQAGQCPAELGVLTVAVPAGGQEDAQC (SEQ ID NO:1072), QLSLLLGEHLLRDQVVEQCDHAHGEH (SEQ ID NO:1073), GS PFDGLHLDLGVAGKGSAQHKSILLHEGLC (SEQ ID NO:1074), and/or HLMDFKIKERSNLLFQTGAGTIELVDQP (SEQ ID NO:1075). Moreover,
- 25 fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
- 30 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

5 This gene is expressed primarily in the greater omentum, and to a lesser extent in gall bladder, stromal bone marrow cells, lymph node, liver, testes, pituitary, and thymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the endocrine, gastrointestinal, and immunological systems, including autoimmune disorders and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, metabolic, immune, hematopoietic, hepatic, reproductive, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 408 as residues: Asn-27 to Leu-47, Gln-81 to Lys-88, Asp-93 to Lys-102, Asn-107 to Leu-116, Met-129 to Glu-141, Glu-150 to Asp-157, Lys-176 to Glu-185, Glu-333 to Tyr-349, Cys-393 to Leu-403, Gln-423 to Gly-429.

The tissue distribution within gastrointestinal, endocrine and immunological tissues, combined with the sequence homology to a conserved collagen motif, indicates that the protein product of this gene is useful for the diagnosis of various autoimmune disorders including, but not limited to, rheumatoid arthritis, lupus erythromatosus, scleroderma, and dermatomyositis. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders

including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:170 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:170, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 161

This gene has homology to the tissue inhibitor of metalloproteinase 2. Such inhibitors are vital to the proper regulation of metalloproteins such as collagenases, which has implications for tissue regeneration and autoimmune disorders (See Genbank Accession No. P16368). When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In addition, this gene maps to chromosome 17, and therefore, may be used as a marker in linkage analysis for chromosome 17 (See Genbank Accession No. P16368).

This gene is expressed primarily in several types of cancers including osteoclastoma, chondrosarcoma, and rhabdomyosarcoma, and to a lesser extent, in non-malignant tissues including synovium, amygdala, testes, and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or integumentary disorders, particularly cancers of bone and cartilage, as well as various autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculoskeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, integumentary, synovium, muscle, fibroids, reproductive, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 409 as residues: Thr-24 to Thr-34.

The tissue distribution in various cancers, combined with the sequence homology to a collagenase inhibitor and the detected GAS biological activity, indicates that the protein product of this gene is useful for the detection of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. The expression of this gene product would also suggest a role in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis, bone cancer, as well as, connective tissue disorders (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and

specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the
5 above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:171 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1989 of SEQ ID NO:171, b is an integer of 15 to 2003, where both a and b correspond to the positions of nucleotide
15 residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 162

20 This gene is homologous to the mitochondrial ATP6 gene, and therefore is likely a homolog of this gene family (See Genbank Accession No. X76197).

This gene is expressed primarily in brain tissue.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample
25 and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, including, but not limited to, neurodegenerative conditions, Down's syndrome, depression, Schizophrenia, and epilepsy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
30 disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded

tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution in brain tissue indicates this gene is useful for diagnosis of various neurological disorders including, but not limited to, brain cancer. Additionally the gene product may be used as a target in the immunotherapy of cancer in the brain as well as for the diagnosis of metabolic disorders such as obesity, Tay-Sachs disease, phenylketonuria and Hurler's Syndrome. Similarly, the protein product
10 of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and
15 infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function.
20 Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies
25 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:172 and may have been publicly available prior to conception
30 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 772 of SEQ ID NO:172, b is an integer of 15 to 786, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 163

The translation product of this gene was found to have homology to the MRS3 and 4 protein of *Saccharomyces cerevisiae* (See Genbank Accession No. gi|3996), which is known to suppress a splice defect in mitochondrial by possibly serving to modulate the cation-solute concentration in mitochondria.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

- 15 DEPCPPPAASCAPPSWRMELRTGSVGSQAVARRMDGDSRDGGGGKDATGSE
DYENLPTSASVSTHMTAGAMAGILEHSVMYPVDSVKTRMQSLSPDKAQYT
SIYGALKKIMRTEASGGPCEASTS (SEQ ID NO:1076),
RMELRTGSVGSQAVARRMDGDSRDGGGGKDATGS (SEQ ID NO:1077),
and/or PVDSVKTRMQSLSPDKAQYTSIYGAL (SEQ ID NO:1078). Moreover,
20 fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
25 of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

- 30 This gene is expressed primarily in placenta, neutrophils, and microvascular
endothelial cells, and to a lesser extent, brain, prostate, spleen, thymus, and bone.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, vascular, or reproductive disorders. Similarly, polypeptides and antibodies
5 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, vascular, endothelial, reproductive, neural,
10 skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 164

The gene encoding the disclosed cDNA is believed to reside on chromosome
20 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in neutrophils, monocytes, bone marrow, and fetal liver.

Polynucleotides and polypeptides of the invention are useful as reagents for
25 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system or hematopoietic disorders including, but not limited to, autoimmune disorders such as lupus, leukemia and immunodeficiency disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
30 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, hepatic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in various immune system tissues indicates that the protein product of this gene is useful for the diagnosis of various immunological disorders such as Hodgkin's lymphoma, arthritis, asthma, immune deficiency diseases
10 such as AIDS, and leukemia. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow
15 reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of
20 various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
25 related to SEQ.ID NO:174 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
30 formula of a-b, where a is any integer between 1 to 1355 of SEQ ID NO:174, b is an integer of 15 to 1369, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 165

5 The translation product of this gene shares sequence homology with dystrophin which is thought to be defective in both Duchene and Becker Muscular Dystrophy.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 10 MKLLGECSSSIDSVKRLEHKLKEEEESLPGFVNLHSTETQTAGVIDRWELLQA
QALSKELRMKQNLQKWQQFNSDLNSIWAWLGDTEEELEQLQRLELSTDIQTI
ELQIKKLKELQKAVDHRKAILSNLCSPEFTQADSKESRDLQDRLXQMNGRW
DRVCSLLEEWGRLLQDALMQCQGFHEMSHGLLLMLENIDRRKNEIVPIDSNL
DAEILQDHHKQLMQIKHELLESQLRVASLQDMSCQLLVNAEGTDCLEAKEK
15 VHVIGNRLKLLLKEVSRHIKELEKLLDVSSSQDLSSWSSADELDTSGSVSPX
SGRSTPNRQKTPRGKCSLSQGPSVSSPHSRSTKGGSDSSLSEXPGRSGRGFL
FRVLRAALPLQLLLLLLIGLACLVPMSEEDYSCALSNNFARSFHPMLRYTNGP
PPL (SEQ ID NO:1079),
MKLLGECSSSIDSVKRLEHKLKEEEESLPGFVNLHSTETQTAGVIDRWELLQA
20 QALSKELRMKQNLQKWQQFNSDLNSIWAWLGDTEEELEQLQRLELSTDIQTI
ELQIK (SEQ ID NO:1080),
KLKELQKAVDHRKAILSNLCSPEFTQADSKESRDLQDRLXQMNGRWDRVC
SLLEEWGRLLQDALMQCQGFHEMSHGLLLMLENIDRRKNEIVPIDSNLDAEIL
QDHHKQLMQIKHELLESQLRVASLQDMSCQL (SEQ ID NO:1081),
25 QDMSCQLLVNAEGTDCLEAKEKVHVIGNRLKLLLKEVSRHIKELEKLLDVSS
SQDLSSWSSADELDTSGSVSPXSGRSTPNRQKTPRGKCSLSQGPSVSSPHS
(SEQ ID NO:1082),
DSSLSEXPGRSGRGFLFRVLRAALPLQLLLLLLIGLACLVPMSEEDYSCALSN
NFARSFHPMLRYTNGPPPL (SEQ ID NO:1083),
30 QRFLPPGSCXLIRGPQCPRVTDPTTGQSLDDSRFQIQQTENIRSKTPTGPELDT
SYKGY (SEQ ID NO:1084),
SISASRLESIGTISFFLLSMFSSIRSKPWLISWKPWHCIRASCSRPRHSSSREHTR

SQRPFICXKRSCRSRLSLLSAWVNSGLQRLMERMMALRWSTAFWSSLSFLIW
 SSMVWMSVLSSRRWSCSNSSSVSPSQAQMLFKSELNCCHFWRFCFILNSLLN
 AWAWRSSSHRSITPAVWVSVLCRLTKPGRLLLLSSSLFTESILLHSPSSF
 M (SEQ ID NO:1085), TAFWSSLSFLIWSSMVWMSVLSSRRWSCSNSSSVS
 5 (SEQ ID NO:1086), LLNAWAWRSSSHRSITPAVWVSVLCRL (SEQ ID NO:1087),
 LARHVLQRGYSELGFQQLMLYLHKLFVMVLKYLCIKVRINRDNFIFPSVNVL
 QHKKQTMAHFMETLALHQGILQQAPLLQQRAHSVPAPIHLXQAILQVPALL
 AVSLGELRAAEIDGEDDGFAVVHSFLELLELFDLELDGLDVSAEFQTLELFQL
 LLRVPQPGPDAVQV (SEQ ID NO:1088),
 10 YSELGFQQLMLYLHKLFVMVLKYLCIKV (SEQ ID NO:1089),
 AMVCFLCWRTLTEGK (SEQ ID NO:1091), and/or
 VHSFLELLELFDLELDGLDVSAEFQTLEL (SEQ ID NO:1090). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 15 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

20 This gene maps to chromosome 6, and therefore, may be used as a marker in
 linkage analysis for chromosome 6 (See Genbank Accession No. N62896).

This gene is expressed in numerous tissues including the heart, kidney, and
 brain.

Polynucleotides and polypeptides of the invention are useful as reagents for
 25 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 musculoskeletal disorders including Muscular Dystrophy and cardiovascular diseases.
 Similarly, polypeptides and antibodies directed to these polypeptides are useful in
 providing immunological probes for differential identification of the tissue(s) or cell
 30 type(s). For a number of disorders of the above tissues or cells, particularly of the
 muscle tissues, expression of this gene at significantly higher or lower levels may be
 routinely detected in certain tissues or cell types (e.g., muscle, heart, and cancerous

and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution in heart, combined with the homology to the human dystrophin gene indicates that the protein product of this gene is useful for the diagnosis and treatment of Muscular Dystrophy and other muscle disorders, particularly musculodegenerative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets
10 for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:175 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
15 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2365 of SEQ ID NO:175, b is an integer of 15 to 2379, where both a and b correspond to the positions of nucleotide
20 residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 166

25 In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:
GAGVGTAMPRVPQSAGGAVTWVGVLSPSSVQGGARPGTVPGTGPGPLPG
LSPAPPPQHPPPLPKLFLCLSLPQDFSLCLSLDPCPSSTSDL (SEQ ID
NO:1092), GTVPGTGPGLPGLSPAPPPQHPPPLPKLFL (SEQ ID NO:1093),
30 APSRCRRSVVQVPYSAFSSCSWTPTALRRGVLLYAGLSTSSASKAQGWHLG
LEYPSGAIMEVRGRGGDRYAQGPSKCWRGCXLVGSGSVTAILCPGWGKAW
DSARHPRTPSRLVSCSTASTPPTPAQAVSPLPLXFPAPGLLSSPLPLLGPLFLY

L (SEQ ID NO:1094), TALRRGVLLYAGLSTSSASKAQGWHCLGLEYPGAIM (SEQ ID NO:1095), AILCPGWGKAWD SARHPRTPSRLVSCSTASTPP (SEQ ID NO:1096),

PPVFMASHRPXGMEPGEWRFVLVHIAFXCAWDLVCEHVSVC SQVRGRGRA
5 GVQGEAE EKREVLGQGXREAE EKQLGQGWGV LRRWSRRQAWKGSWGAW
HCPRPCPTLDRGWL (SEQ ID NO:1097), and/or
HVSVC SQVRGRGRAGVQGEAE EKREVLGQ (SEQ ID NO:1098). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in human cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
diseases of the central nervous system, including Alzheimer's Disease, Parkinson's
20 Disease, ALS, and mental illnesses. Similarly, polypeptides and antibodies directed
to these polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the central nervous system, expression of this gene at
significantly higher or lower levels may be routinely detected in certain tissues or cell
25 types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,
serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
taken from an individual having such a disorder, relative to the standard gene
expression level, i.e., the expression level in healthy tissue or bodily fluid from an
individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 414 as residues: Pro-20 to Gly-26, Leu-37 to Pro-42, His-57 to Gly-63.

The tissue distribution in human cerebellum indicates that the protein products of this gene are useful for the treatment/diagnosis of diseases of the central nervous system and may protect or enhance survival of neuronal cells by slowing progression of neurodegenerative diseases. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:176 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1334 of SEQ ID NO:176, b is an integer of 15 to 1348, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 167

In specific embodiments, polypeptides of the invention comprise, or
5 alternatively consists of, the following amino acid sequence:
MKLLICGNYLAPSHSESSRRCCLLCFYPLCLEINFGMKVFLSMPFLVLFQSLIQ
ED (SEQ ID NO:1099). Moreover, fragments and variants of this polypeptide (such
as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
10 encoded by the polynucleotide which hybridize, under stringent conditions, to the
polynucleotide encoding this polypeptide are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
invention. Polynucleotides encoding this polypeptide are also encompassed by the
invention.

15 The gene encoding the disclosed cDNA is believed to reside on chromosome
15. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 15.

This gene is expressed primarily in human testes tumor, and to a lesser extent,
in normal human testes.

20 Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
diseases of the testes, particularly cancer, and other reproductive disorders. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
25 immunological probes for differential identification of the tissue(s) or cell type(s).
For a number of disorders of the above tissues or cells, particularly of the male
reproductive tissues, expression of this gene at significantly higher or lower levels
may be routinely detected in certain tissues or cell types (e.g., reproductive, testicular,
and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal
30 fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human testicular tissue indicates that the protein products of this gene are useful for the treatment/diagnosis of reproductive diseases including cancers. Moreover, the protein may possibly have utility as a contraceptive or may be used to ameliorate disorders related to aberrant male secondary characteristics (e.g. hair, etc.). Protein, as well as, antibodies directed against the protein may, show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:177 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1488 of SEQ ID NO:177, b is an integer of 15 to 1502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 168

The translation product of this gene was found to have homology to the gar2 gene product of Schizosaccharomyces pombe, which is thought to be involved in protein metabolism (See Genbank Accession No. gi|663262).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:
 FSSPQGLKFRSKSSLANYLHKNGETSLKPEDFDFTVLSKRGIKSRYKDCS (SEQ
 ID NO:1100),
 ELLCYICWKNTGLFSFFLSVFRGMVSSVKSFLVGEQLLSISEPRFKMSVCKCSF
 LSTTSTFVPISSDSKKVSSYFSLCESLAEQNLFMMPEVFCSEQKFDPELNDLSF

FFTRLFSSLVTLRVSPHAPASEMQTVLS (SEQ ID NO:1101), and/or
TFVPISSDSKKVSSYFSLCSESLAEQNLFMMPEVFC (SEQ ID NO:1102).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,
5 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3:

This gene is expressed primarily in fetal liver.

Polynucleotides and polypeptides of the invention are useful as reagents for
15 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic disorders, in addition to conditions affecting hematopoietic development and metabolic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
20 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, and fetal hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, metabolic, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, bile, plasma,
25 urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
30 NO: 416 as residues: His-7 to Trp-17, Leu-19 to Lys-27, Pro-33 to Gly-44, Lys-68 to Gly-74, Lys-85 to Cys-95.

The tissue distribution in liver, combined with the homology to the gar2 protein, indicates that the protein products of this gene are useful for the treatment/diagnosis of diseases of the developing liver and hematopoietic system, and act as a growth differentiation factor for hematopoietic stem cells. Moreover, the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition, the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders, and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:178 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1623 of SEQ ID NO:178, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 169

The polypeptide encoded by this gene is believed to be a membrane bound receptor.

Additionally, the extracellular domain of this polypeptide is expected to comprise the following amino acid sequence:

RILLVKYSANEENKYDYLPTTVNVCSELVKLVFCVLVSFCVIKKDHQSRNLK
YASWKEFSDFMKWSIPAFLYFLDNLIVFYVLSYLQPAMAVIFS NFSIT TALLF

RIVLKXRLNWIQWASLLTLFLSIVALTAGTKTLQHNLAGRGFHHD AFFSPSNS
 CLLFRNECPRKDNCTAKEWTFPEAKWNTTARVFSHIRLGMGHVLIIVQCFISS
 MANYNEKILKEGNQLTEXIFIQNSKLYFFGILFNGLTLGLQRSNRDQIKNCGF
 FYGHS (SEQ ID NO:1103), TVNVCESELVKLVFCVLVSFCVIKKDHQSRN (SEQ
 5 ID NO:1104), LIVFYVLSYLQPAMAVIFS NFSI TTALLFR (SEQ ID NO:1105),
 FFSP SNSCLLFRNECPRKDNCTAKEWT (SEQ ID NO:1106), and/or
 YFFGILFNGLTL GLQRSNRDQIKNCGFF (SEQ ID NO:1107). Accordingly,
 preferred polypeptides encoded by this gene comprise the extracellular domain, as
 shown above. It will be recognized, however, that deletions of either end of the
 10 extracellular domain up to the first cysteine from the N-terminus and the first cysteine
 of the C-terminus, is expected to retain the biological functions of the full-length
 extracellular domain, because the cysteines are thought to be responsible for
 providing secondary structure to the molecule. Thus, deletions of one or more amino
 acids from either end (or both ends) of the extracellular domain are contemplated. Of
 15 course, further deletions including the cysteines are also contemplated as useful, as
 such polypeptides is expected to have immunological properties such as the ability to
 evoke an immune response. Polynucleotides encoding all of the foregoing
 polypeptides also encompassed by the invention.

This gene is expressed primarily in human osteoclastoma, and to a lesser
 20 extent, in hippocampus and chondrosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for
 differential identification of the tissue(s) or cell type(s) present in a biological sample
 and for diagnosis of diseases and conditions which include, but are not limited to,
 skeletal or connective tissue disorders, particularly cancers. Similarly, polypeptides
 25 and antibodies directed to these polypeptides are useful in providing immunological
 probes for differential identification of the tissue(s) or cell type(s). For a number of
 disorders of the above tissues or cells, particularly of the skeletal system, expression
 of this gene at significantly higher or lower levels may be routinely detected in certain
 tissues or cell types (e.g., skeletal, neural, immune, connective, and cancerous and
 30 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid
 and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 417 as residues: Met-1 to Cys-6, Ala-41 to Tyr-49, Lys-76 to Lys-84.

5 The tissue distribution in osteoclastoma and chondrosarcoma indicates that the protein products of this gene are useful for the diagnosis of cancers of the bone and connective tissues, and may act as growth factors for cells involved in bone or connective tissue growth. Moreover, this gene product may show utility in the detection and treatment of disorders and conditions affecting the skeletal system, in
10 particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis, as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e.
15 spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:179 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2897 of SEQ ID NO:179, b is an integer of 15 to 2911, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 170

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: NSVPNLQTLAVLTEAIGPEPAIPRXPREPPVATSTPATPSAGPQPLPTGTVLVPG GPAPPCLGEAWALLLPPCRPSLTSCFWSPRPSWKETGV (SEQ ID NO:1108),
 5 VTAGRVGGGGPMPPQGKVGQDPQGPARSRLGGAGARQRVWQVWTWQ QAAPGGXGGWRALGQWPQ (SEQ ID NO:1109), STPATPSAGPQPLPTGTVLVPGGPAP (SEQ ID NO:1110), and/or QDPQGPARSRLGGAGARQR (SEQ ID NO:1111). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,
 10 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are
 15 also encompassed by the invention.

This gene is expressed primarily in hematopoietic progenitor cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
 20 hematopoietic or immune disorders, particularly cancer and autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the blood/circulatory system, expression of this gene at significantly higher or lower
 25 levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
 30 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 418 as residues: Gln-4 to His-10, Pro-25 to His-32.

The tissue distribution in hematopoietic progenitor cells indicates that the protein products of this gene are useful for diagnosis of diseases involving growth differentiation of hematopoietic cells. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as

5 anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such

10 as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed

15 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:180 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 505 of SEQ ID NO:180, b is an integer of 15 to 519, where both a and b correspond to the positions of nucleotide

25 residues shown in SEQ ID NO:180, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 171

30 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
 ALQLAFYPD AVEEWLEENVHPSLQRLQXLLQDLSEVSAPP (SEQ ID

NO:1112), CHPPALAGTLLRTPEGRAHARGLLLEAGGA (SEQ ID NO:1113),
 GSSSTRSWFSTSSPQRSASWHSGAPSCRSWRLPCSWLSTRMPWRSGWRKTCT
 PACSGCK (SEQ ID NO: 1114),
 ASTLQPSLSPSSPPLXPPVETAVXSRALRREGAGSFPGSNILALVTQVSLHLRSS
 5 VDALLEGNRYVTGWFSFYHRQRKLIHPV (SEQ ID NO:1115),
 PLGPEKAGLAXPLVXHAARPCPSTSLQSCPSLXXEPXXPPRSXVISGGFDE
 DVKAKVENLLGISSLEKTDVPRQAPCSPPCPLLPLPFXRPWRQLFSAGLSAGR
 GPAPSLAATSLPLSHKSASICAALWMRCWRATGMSLAGSAPTTASGSSSTRS
 WFSTSSPQRSASWHSGAPSCRSWRLPCSWLSTRMPWRSGWRKTCTPACSGC
 10 KLCCRTSARCLPPRCHPPALAGTLLRTPEGRAHARGLLLEAGGALXXXXAW
 AIRPTWASCPLAQCLAHTQFLRALGSPWGRD (SEQ ID NO:1116),
 FQEDLMKMLKRKWRTFSGFPAWKKRTLLGKHPAALVPFFPSPSPARGDSCX
 QQGSPQGGGRLLPWQQHPCPCHTSQPPSAQLCGCAAGGQVCHWLQVPLPP
 PAEAHPPGHGSAHPARSAQPPGTVEHPRAGAGGCPAAGFLPGCRGGVAGGK
 15 RAPQPAAXSAAGPQRGVCPPAATHQPWQGRCSGPLRGELMPGGSCWRL
 GGLCXXXWPGQYGRGRRALWPSSVLPTLSS (SEQ ID NO:1117),
 ALPSGVLSNVPARAGGWQRGGRHLAEVLQQSLQPLQAGVHVFLQPLLHGIR
 VESQLQGSLLHEGAPLCQEAERCGLDVLNHDRVDELPLAVVGAEPASDIP
 VALQQRHRAAQMEADLCDKGKDVAAREGAGPLPAESPAENSC LHGRXKGR
 20 GRRGQGGGLQGACLTGSVFSRLEIPRRFSTFALTSSSNPPEITXXRGGXXGSXXR
 EGLHWDCLVLGHGRAAWXTNGQANPAFSGPKG (SEQ ID NO:1118),
 RQLFSAGLSAGRGPAPSLAATSLPLSHKS (SEQ ID NO:1119),
 ELPLAVVGAEPASDIPVALQQRHRAAQ (SEQ ID NO:1120), and/or
 QPPGTVEHPRAGAGGCPAAGFLPGCRG (SEQ ID NO:1121). Moreover,
 25 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 30 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

The protein product of this gene shares sequence homology with metallothionines. Thus, polypeptides encoded by this gene are expected to have metallothionine activity. Furthermore, such activities are known in the art and described elsewhere herein.

5. This gene is expressed primarily in kidney cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal disorders, particularly diseases of the kidney including cancer and renal
10 dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal,
15 urogenital, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 20 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 419 as residues: Ser-47 to Gln-52.

The tissue distribution in kidney cortex indicates that the protein product of this gene is useful for the treatment/diagnosis of diseases of the kidney, including kidney failure. Moreover, this gene or gene product could be used in the treatment
25 and/or detection of kidney diseases including nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies
30 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:181 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 954 of SEQ ID NO:181, b is an integer of 15 to 968, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 172

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: SVFERTNEFRDVLWSSI (SEQ ID NO:1122),
 GVVQVTFMSSVSRVTWGCQPSICPGAPPAALAGGLRLLFERELFGLPVSSPL
 ICSFLEHHPRTSPPPSDCELLEGRSCVLLFFILSPEPCTDPMW (SEQ ID
 NO:1123),
 SKQIHSFVHSFIHLFNTHLLSTYHIPGSVQSGDRKMNRRTQLLPSRSSQSDGG
 GDVLGWCSKKEQIRGEETGRPNSSLKRSLRPPARAAAGGAPGQMLG (SEQ
 ID NO:1124), VTWGCQPSICPGAPPAALAGGLRLLFE (SEQ ID NO:1125).
 and/or EQIRGEETGRPNSSLKRSLRPP (SEQ ID NO:1126). Moreover, fragments
 and variants of these polypeptides (such as, for example, fragments as described
 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%
 identical to these polypeptides and polypeptides encoded by the polynucleotide which
 hybridizes, under stringent conditions, to the polynucleotide encoding these
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
 of the invention are also encompassed by the invention. Polynucleotides encoding
 these polypeptides are also encompassed by the invention.

This gene is expressed primarily in 12 week old early stage human.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these

5 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing embryo, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, and cancerous and wounded tissues) or bodily fluids (e.g.,

10 lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

15 NO: 420 as residues: Gln-31 to Thr-43, Gly-51 to Ser-58, Pro-65 to Pro-72.

The tissue distribution in embryonic tissue indicates that the protein product of this gene is useful for treatment/diagnosis of developmental conditions. The gene may be involved in vital organ development in the early stage, especially hematopoiesis, the cardiovascular system, and neural development. Moreover,

20 expression within embryonic tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again

25 be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

30 related to SEQ ID NO:182 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1114 of SEQ ID NO:182, b is an integer of 15 to 1128, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 173

The translation product of this gene shares sequence homology with TGN38, an integral membrane protein previously shown to be predominantly localized to the trans-Golgi network (TGN) of cells. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in developing embryo, and to a lesser extent, in cancer tissues including lymphoma, endometrial, prostate and colon.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, reproductive, immune, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 421 as residues: His-65 to Ser-72, Pro-82 to Gly-91, Pro-98 to Glu-118, Ser-126 to Gly-166, Pro-180 to Asp-188, Tyr-209 to Lys-214, Gln-220 to Leu-228.

5 The tissue distribution in the embryo, combined with the homology to an integral membrane protein indicates that the protein product of this gene is useful for the diagnosis of cancers and developmental abnormalities where aberrant expression relates to an abnormality. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of
10 cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed
15 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:183 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2262 of SEQ ID NO:183, b is an integer of 15 to 2276, where both a and b correspond to the positions of nucleotide
25 residues shown in SEQ ID NO:183, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 174

30 The translation product of this gene shares sequence homology with a dnaJ heat shock protein from E. coli which is allelic to sec63, a gene that affects transit of nascent secretory proteins across the endoplasmic reticulum in yeast.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

QWEHLLLLPHLLRGAHRDPGDILPLAPRSECRANSIKEYQKSIWKVYVVRRLRL
LKPQPNIPTVKKIVLLAGWALFLFLAYKVSKTREYQEYNPYEVLNLDPGAT

5 VAEIKKQYRLLSLKYHPDKGGDEV (SEQ ID NO:1127),

EERGGGGGAMAGQQFQYDDSGNTFFYFLTSFVGLIVIPATYYLWPRDQNAEQ
IRLKNIRKVYGRG (SEQ ID NO:1128),

RLYTGCVIFDLVSNRALSFRCLCCNSCHSASSSLFCFSSCSLSSESLSLPSSFSL
WESLLVSSSSSESPLSETSSSSSFTAASFPTTPFACFCFCCFDCGNSTGVGFFFK

10 GFFFFDLAVFLGPLLFCCHPPFVLFLLVSPCPSSAGCSSAAQMDCSFSNTSAIV

CLVNLTNTVTKDPTVMALLSSSSNTCDFISMVTYGKLPRTAITSSYFSSSRKCS
RV (SEQ ID NO:1129), YQKSIWKVYVVRLLKPQPNIPTVKKIVLLAGW

(SEQ ID NO:1130), and/or CHPPFVLFLLVSPCPSSAGCSSAAQMDCSFSNTSA
(SEQ ID NO:1131). Moreover, fragments and variants of these polypeptides (such

15 as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides

encoded by the polynucleotide which hybridizes, under stringent conditions, to the
polynucleotide encoding these polypeptides) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the

20 invention. Polynucleotides encoding these polypeptides are also encompassed by the
invention.

This gene is expressed primarily in Hodgkin's lymphoma, and to a lesser
extent, in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for
25 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
immune or hematopoietic disorders, particularly cancer. Similarly, polypeptides and
antibodies directed to these polypeptides are useful in providing immunological
probes for differential identification of the tissue(s) or cell type(s). For a number of
30 disorders of the above tissues or cells, particularly of the immune system, expression
of this gene at significantly higher or lower levels may be routinely detected in certain
tissues or cell types (e.g., immune, hematopoietic, reproductive, testicular, and

cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
5 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 422 as residues: Val-37 to Pro-49, His-76 to Asp-82, Thr-97 to Trp-105, Arg-158 to Asp-165, Glu-199 to Asp-214, Asn-229 to Pro-236, Thr-261 to Gln-266, Arg-292 to Glu-298, Glu-335 to Lys-351, Glu-372 to Glu-377, Leu-398 to Asn-405, Glu-437
10 to Pro-480, Gln-487 to Gln-495, Lys-507 to Ala-555, Ser-563 to Arg-569, Pro-588 to Glu-593, Lys-618 to Val-623, Pro-630 to Asn-635, Ser-644 to Gly-649, Lys-664 to Trp-673, Gly-679 to Phe-689, Asp-691 to Asp-704.

The tissue distribution in Hodgkin's lymphoma, combined with the homology to dnaJ and sec63 indicates that the protein product of this gene is useful as a
15 diagnostic for cancer, that the protein may be useful in regulating gene expression levels, and that it is essential for normal protein metabolism. Therefore, protein products of this gene may show utility as an anticancer agent, or even serve to protect from viral or bacterial infections, based upon its homologous function as a protein chaperone. Protein, as well as, antibodies directed against the protein may show
20 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:184 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3360 of SEQ ID NO:184, b is an integer of 15 to 3374, where both a and b correspond to the positions of nucleotide
30 residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 175

The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5. Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of chondrocytes to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both chondrocytes, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating chondrocytes.

This gene is expressed primarily in endothelial cells, and to a lesser extent, in bone marrow stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, endothelial, or vascular disorders, such as diseases involving angiogenic abnormalities including diabetic retinopathy, macular degeneration, and other diseases including arteriosclerosis and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, endothelial, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial cells indicates that the protein products of this gene are useful for treating diseases where an increase or decrease in angiogenesis is indicated and as a factor in the wound healing process. In addition,

the protein product of this gene may show utility in the treatment, detection, and/or prevention of a variety of vascular disorders, which include, but are not limited to microvascular disease, embolism, thrombosis, atherosclerosis, aneurysm, or stroke. Moreover, the protein product of this gene is useful for the treatment and diagnosis of

5 hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in

10 lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as

15 a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:185 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1323 of SEQ ID NO:185, b is an integer of 15 to 1337, where both a and b correspond to the positions of nucleotide

25 residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 176

30 The translation product of this gene shares sequence homology with both the RIC and MAT8 proteins (mouse), which are thought to be important in regulating

chloride conductance in cells by modulating the response mediated by cAMP and protein kinase C to extracellular signals.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

- 5 GTSLDAAATAASLSPRGCRLRTPSSD (SEQ ID NO:1132),
QIQRHTRAPKQLIPLMTPRRSLRDHPQAQTSRQTPRPSSHLVFMRMTPSSMM
NTPSGNGGCWSQLCCSSQASSSSPVASAGSCPGYAGIAGESIRNRS (SEQ ID
NO:1133), PRRSLRDHPQAQTSRQTPRPSSHLVFM (SEQ ID NO:1134),
THPPETGAVGRSCAVHHRHHHPHQWQVQAAVPVMPESLQVSPSETGADNXL
10 GTRRPSPLPAHRAQPPASPRRAWPEREDTDDEAGARAAGPSLLPPPTLPAPEG
YLAPWGLSLKLSPLLRQKVKHCGLC (SEQ ID NO:1135),
PESLQVSPSETGADNXLGTRRPSPLPAHRAQPPASP (SEQ ID NO:1136),
GTAPKAPGSLQGRAGLGEVGDSRQPWLQLHHLCLPSLARLFEGMQEAGHG
ELAGGLVFGCPAGCQLFLMDSPAMPA (SEQ ID NO:1137),
15 GEVGDSRQPWLQLHHLCLPSLARLFEGMQEAGH (SEQ ID NO:1138),
GSGGLSGRLCLGMVSQRASWCHQWDELLWCSCVSLDLSLEAHPFLPVAGSG
SGVVVFHQQARLGLERWAGVLCRLHLGLVSGPECP (SEQ ID NO:1139),
and/or QWDELLWCSCVSLDLSLEAHPFLPVAGSGSGVVVFHQQARL (SEQ ID
NO:1140). Moreover, fragments and variants of these polypeptides (such as, for
20 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,
96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by
the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
encoding these polypeptides) are encompassed by the invention. Antibodies that bind
polypeptides of the invention are also encompassed by the invention. Polynucleotides
25 encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

- 30 This gene is expressed primarily in amniotic cells and hematopoietic cells
including macrophages, neutrophils, T cells, TNF induced aortic endothelium, and to
a lesser extent in testes, TNF induced epithelial cells, and smooth muscle.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly inflammatory responses mediated by T cells, macrophages, and/or neutrophils, particularly those involving TNF, and also cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 424 as residues: Thr-19 to Ala-33, Leu-54 to Asp-82, Pro-89 to Ala-97, Pro-100 to Lys-125, Ser-127 to Phe-135, Gly-164 to Leu-169, Cys-173 to Arg-178.

The tissue distribution in hematopoietic cells, combined with the homology to the RIC and mat-8 genes, indicates that the protein product of this gene is useful for modifying inflammatory responses to cytokines such as TNF, and thus modifying the duration and/or severity of inflammation. Polynucleotides and polypeptides derived from this gene are thought to be useful in the diagnosis and treatment of cancer. The protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and

in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:186 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 927 of SEQ ID NO:186, b is an integer of 15 to 941, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 177

This gene is expressed primarily in endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular disorders, including vascular restenosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
25 disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, endothelial, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
30 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial tissue indicates that the protein product of this gene is useful for treating diseases associated with vascular responses to injury such as vascular restenosis following angioplasty. Moreover, the protein product of this gene is useful for the treatment, detection, and/or prevention of a variety of other
5 vascular disorders, which include, but are not limited to microvascular disease, embolism, thrombosis, atherosclerosis, aneurysm, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:187 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:187, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 178

This gene appears to be chimeric. There are two ORFs of interest. The first ORF-1 encodes a polypeptide preferably comprising one of the following polypeptide
25 sequences:

MRPDWKAGAGPGGPPQKPAPSSQRKPPARPSAAAAIAVAAEEERRLRQR
NRLRLEEDKPAVERCLEELVFGDVENDEALLRRLRGPRVQEHEDSGDSEVE
NEAKGNFPPQKKPVWDEEDEDEEMVDMNNRFRKDDMMKNASESKLSKD
NLKKRLKEEFQHAMGGVPAWAETTKRKTSSDDESEDEDDLLQRTGNFISTS
30 TSLPRGILKMKNQCQHANAERPTVARISICAVPSRCTDCDGCWD (SEQ ID
NO:1141); and/or
CLEELVFGDVENDEALLRRLRGPRVQEHEDSGDSEVENEAKGNFPPQKKPV

WVDEEDEDEEMVDMNNRFRKDMMKNA SESKLSKDNLKKRLKEEFQHAM
GGVPAWAETTKRKTSSDDESEEDD LQRTGNFISTSTSLPRGILKMKN CQH
ANAERPTVARISICAVPSRCTDCDGC (SEQ ID NO:1142). The second ORF
(ORF-2) encodes a polypeptide preferably comprising one of the following

5 polypeptide sequences:

LKEKIVRSFEVSPDGSFLLINGIAGYLHLLAMKTKELIGSMKINGRVAASTFSS
DSKKVYASSGDGEVYVWDVNSRKCLNRFVDEGSLYGLSIATSRNGQYVACG
SNCGVVNIYNQDSCLQETNPKPIKAIMNLVTGVTSLTFNPTTEILAIASEKMKE
AVRLVHLPSCTVFSNFPVIKNKNISHVHTMDFSPRSGYFALGNEKGKALMYR

10 LHHYSDF (SEQ ID NO:1143); and/or

KINGRVAASTFSSDSKKVYASSGDGEVYVWDVNSRKCLNRFVDEGSLYGLSI
ATSRNGQYVACGSNCGVVNIYNQDSCLQETNPKPIKAIMNLVTGVTSLTFNP
TTEILAIASEKMKEAVRLVHLPSCTVFSNFPVIKNKNISHVHTMDFSPRSGYFA
LGNEKGKAL (SEQ ID NO:1144).

15 In specific embodiments, polypeptides of the invention comprise, or alternatively
consist of, the following amino acid sequences:

WLLGLDNAVSLFQVDGKTNP KIQSIYLERFPIFKACFSANGEEVLATSTHSKV
LYVYD (SEQ ID NO:1145), LVFGDVENDE DALLRRLRGPRVQ (SEQ ID
NO:1146), KNA SESKLSKDNLKKRLKEEFQHAMGGVP (SEQ ID NO:1147),

20 and/or SLPRGILKMKN CQHANAERPTVA (SEQ ID NO:1148). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
25 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
of the invention are also encompassed by the invention. Polynucleotides encoding
these polypeptides are also encompassed by the invention.

The translation product of this gene shares homology with the transcriptional
repressor TUP1 of *Candida albicans* (See Genbank Accession No. gi|2245634
30 (AF005741)), which is thought to modulate the expression levels of cellular filament
and may implicate this protein as serving a useful role in the amelioration of
proliferating cells and tissues.

This gene is expressed primarily in epididymus and endometrial tumors, and to a lesser extent, in T cell lymphoma and cell lines derived from colon cancer.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive or developmental conditions, which include tumors of the reproductive organs, including testis and endometrial cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 426 as residues: Ser-67 to Lys-72, Val-87 to Leu-93, Tyr-128 to Pro-141, Asp-204 to Gly-210.

The tissue distribution in reproductive tissue cancers, combined with the homology to a transcriptional repressor protein, indicates that the protein products of this gene are useful for treating tumors of the endometrium or epithelial tumors of the reproductive system. Moreover, the protein may also be useful as a contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:188 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1834 of SEQ ID NO:188, b is an integer of 15 to 1848, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 179

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MRILQLILLALATGLVGGETRIKGFECKLHSQPWQAALFEKTRLLCGATLIAP
 RWLLTAAHCLKPRYIVHLGQHNLQKEEGCEQTRTATESFPHPGFNNSLPNKD
 HRNDIMLVKMASPVSTITWAVRPLTLSSRCVTAGTSCSFPAGAARPDPSYACLT
 PCDAPTSPSLSTRSVRTPTPATSQTPWCVPACRKGARTPARVTPGALWSVTSL
 15 FKALSPGARIRVRSPESLVSTRKSANMWTGSRRR (SEQ ID NO:1149);
 ETRIKGFECKLHSQPWQAALFEKTRLLCGATLIAPRWLLTAAHCLKPRYIVH
 LGQHNLQKEEGCEQTRTATESFPHPGFNNSLPNKDHRNDIMLVKMASPVSTIT
 WAVRPLTLSSRCVTAGTSCSFPAGAARPDPSYACLT
 PCDAPTSPSLSTRSVRTP
 TPATSQTPWCVPACRKGARTPARVTPGALWSVTSLFKALSPGARIRVRSPESL
 20 VSTRKSANMWTGSRRR (SEQ ID NO:1150); and/or
 CKLHSQPWQAALFEKTRLLCGATLIAPRWLLTAAHCLKPRYIVHLGQHNLQK
 EEGCEQTRTATESFPHPGFNNS (SEQ ID NO:1151). Moreover, fragments and
 variants of these polypeptides (such as, for example, fragments as described herein,
 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
 25 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes;
 under stringent conditions, to the polynucleotide encoding these polypeptides) are
 encompassed by the invention. Antibodies that bind polypeptides of the invention are
 also encompassed by the invention. Polynucleotides encoding these polypeptides are
 also encompassed by the invention.

30 The translation product of this gene shares sequence homology with
 neuropsin, a novel serine protease, which is thought to be important in modulating
 extracellular signaling pathways in the brain. Owing to the structural similarity to

other serine proteases, the protein products of this gene are expected to have serine protease activity which may be assayed by methods known in the art and described elsewhere herein. Moreover, this protein has been shown to also have homology to PSA (prostate specific antigen). PSA is a serum marker for prostate cancer and it is a member of the kallikrein family. The members of the kallikrein family are secreted serine proteases and some of them are good tissue specific markers. This new member of the kallikrein family has been detected twice in endometrial tumor cDNA library and therefore is a good candidate as a serum marker for endometrial tumor.

This gene is expressed primarily in endometrial tumor, and to a lesser extent, in colon cancer, benign hypertrophic prostate, and thymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, immune, or endocrine disorders, particularly cancers of the endometrium or colon and benign hypertrophy of the prostate. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urogenital or reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, immune, endocrine, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 427 as residues: Glu-27 to Trp-35, Leu-77 to Ala-89, Pro-96 to Asn-109, Ser-149 to Arg-156, Gln-172 to Ile-182, Glu-193 to Gly-204, Glu-245 to Asn-250.

The tissue distribution in proliferative reproductive tissues, combined with the homology to serine proteases indicates that the protein product of this gene is useful for diagnosing, treating, and/or preventing hyperproliferative disorders such as cancer of the endometrium or colon and hyperplasia of the prostate. Similarly, expression

within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern
5 formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:189 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1278 of SEQ ID NO:189, b is an integer of 15 to 1292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 180

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
25 VLQGRYFSPILEMRRLRPEGXXNLPGGSSRAQKEPRQDLTLVLWPHCPHFAMT
RSYVPTKQCMVQGSFYCIFYKGPVQNWNC (SEQ ID NO:1152), and/or CPRRRT
CVRVEKSRPFQCQLHSIS (SEQ ID NO:1153). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
30 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are

also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly neurodegenerative conditions, in addition to identifying and expanding stem cells in the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 428 as residues: Met-1 to Lys-9, Glu-26 to Lys-37, Lys-39 to Lys-48.

The tissue distribution in fetal brain indicates that the protein products of this gene are useful for detecting and expanding stem cell populations in the (or of the) central nervous system. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene

product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:190 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 892 of SEQ ID NO:190, b is an integer of 15 to 906, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 181

In specific embodiments, polypeptides of the invention comprise, or alternatively
20 consist of, the following amino acid sequences: PKEPGVPE (SEQ ID NO:1154), LQLKPRDPFSTLGPNAVLS PQRLVLETLSKLSIQDNNVDLILATPPFSRLEKLY STMVRFLSDRKNPVCRRWLWYC WPTWLRGTAWQLVPLQCRRAVSATSWAS (SEQ ID NO:1155), RDPFSTLGPNAVLS PQRLVLETLSKLS (SEQ ID NO:1156), EVISGLFIQSRRRERGQGVVGSHMILWGKSLFFFSPQRLTKNIFKNYSLLLTQR
25 FLFPCETLLLQYVYSIRCTVQYMKGSTLYCTGLSSEQGLFTTANFLAPARL (SEQ ID NO:1157), and/or IRCTVQYMKGSTLYCTGLSSEQG (SEQ ID NO:1158). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
30 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind

polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in early stage human brain, fetal liver/spleen, and stromal cells.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities, neural, immune, or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g.,
15 lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
20 NO: 429 as residues: Gln-42 to Gln-47, Gln-54 to Pro-60.

The tissue distribution in embryonic brain and fetal liver indicates that the protein products of this gene play a role in the development of the central nervous and hematopoietic systems. Therefore this gene and its products are useful for diagnosing or treating developmental abnormalities of the central nervous system. Moreover, the
25 protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of
30 neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in

the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:191 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1927 of SEQ ID NO:191, b is an integer of 15 to 1941, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 182

In specific embodiments, polypeptides of the invention comprise, or
20 alternatively consists of, an amino acid sequence selected from the group:
MPIIDQVNPETHDFMQSAEVTGTFALSWLITWFGHVLSDFRHVVRLYDFFLAC
HPLMPIYFAAVIVLYREQEVLDCDCDMASVHLLSQIPQDLPYETLISRXETFL
FSFPHPNLLGRPLPNSKLRGRQPLLSKTLSTWHQPSRGLIWCCGSGXRGLLRPE
DRTKDVLTKPRTNRFVKLAVMGLTVALGAAALAVVKSALWAPKFQLQLFP
25 (SEQ ID NO:1159; "ORF-1"); or
CPEFFIPATLPCPFVFAFTSEASSRAYLTQRGPGGLAQNLMLPLVGFWMGSLP
PPWCWRKWVSEACSCFC (SEQ ID NO:1160; "ORF-2"). Moreover, fragments
and variants of these polypeptides (such as, for example, fragments as described
herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%
30 identical to these polypeptides and polypeptides encoded by the polynucleotide which
hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides

of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

ORF-2 is structurally similar to various TGF-beta family members. Thus, this polypeptide is expected to have a variety of activities in the modulation of cell growth and proliferation.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

CRQAGAVRGHPMFQFTFYGVTXRFPVTRAAQAQQVAKAAASFRNPLPPTPG
RWQRAHPKAHWERHKILCQAPRSPLCQVGSATGL (SEQ ID NO:1161),

10 HILNYLMPIIDQVNPELHDFMQSAEVGTIFALSWLITWFGHVLSDFRHVVRLY
DFFLACHPLMPIYFAAVIVLYREQEVLDCDCDMASVHLLSQIPQDLPYETLIS
RXETFLFSFPHPNLLGRPLPNSKLRGRQPLLSKTLSTWHQPSRGLIWCCGSGXR
GLLRPEDRTKDVLTTPRTNRFVKLAVMGLTVALGAAALAVVKSALWAPKF
QLQLFP (SEQ ID NO:1162), AEVGTIFALSWLITWFGHVLSDFRHVVRLYD
15 (SEQ ID NO:1163), and/or VLTTPRTNRFVKLAVMGLTVALGAAALAVVKS
(SEQ ID NO:1164). Moreover, fragments and variants of these polypeptides (such
as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
encoded by the polynucleotide which hybridizes, under stringent conditions, to the
20 polynucleotide encoding these polypeptides) are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
invention. Polynucleotides encoding these polypeptides are also encompassed by the
invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome.
25 20. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 20.

This gene is expressed primarily in osteoclastoma, microvascular
endothelium, and bone marrow derived cell lines.

Polynucleotides and polypeptides of the invention are useful as reagents for
30 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
skeletal, vascular, or hematological diseases, particularly those involving aberrant

proliferation of stem cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at

5 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, vascular, immune, hematological, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in

10 healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 430 as residues: Ser-33 to Ala-39.

The tissue distribution in bone marrow and endothelial cells indicates that the protein products of this gene is useful for treating disorders of the progenitors of the

15 immune system. Applications include in vivo expansion of progenitor cells, ex vivo expansion of progenitor cells, or the treatment of tumors of the circulatory system, such as lymphomas. Moreover, the protein product of this gene may also show utility in either the enhancement or inhibition of immune cell localization or targeting at sites of inflammation or injury. The protein product of this gene may be useful in the

20 treatment, detection, and/or prevention of a variety of vascular disorders, which include, but are not limited to microvascular disease, embolism, aneurysm, atherosclerosis, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:192 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2104 of SEQ ID NO:192, b is an

integer of 15 to 2118, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 183

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: GFGSVSAAGRRSGGTWQPVQ (SEQ ID NO:1165), PGGLAVG SRW WSRSLT
 10 (SEQ ID NO:1166), LEPSRQRRPRRRGGTSRPETDQRAKCWRQL (SEQ ID NO:1167), VCLRCQNRMEN (SEQ ID NO:1168), MAACTARRPGRGQPLVVPVADXGPVAKAALCAAXAGAFSPASTTTTRRHLS SRNRPEGKVLETVGVFEPKQNGKYETGQLFLHSIFGYRGVVLPFWQARLXD RDVASAAPEKAENPAGHGSKEVKGKTHYYQVLIDARDCPHISQRSQTEAVT
 15 FLANHDDSRALYAIPGLDYVSHEDILPYTSTDQVPIQHELPERFLLYDQTKAPP FVARETLRAWQEKNHFWLELSDVHRETTENIRVTVIPFYMGMREAQNSHVY WWRYCIRLENLSDSDVVQLRERHWRIFSLSGTLETVRGRGVVGREPVSKEQP AFQYSSHVSLQASSGHMWGTFRFERPDGSHFDVRIPPSLESNKDEKTPPSGL HW (SEQ ID NO:1169), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA
 20 (SEQ ID NO:1170), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID NO:1171), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID NO:1172), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID NO:1173), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID NO:1174), VLETVGVFEPKQNGKYETGQLFLHSIFGYRGVVL (SEQ ID
 25 NO:1175), GLDYVSHEDILPYTST (SEQ ID NO:1176), DVHRETTENIRVTVIPFYM (SEQ ID NO:1177), WWRYCIRLENLSDSDVVQLRER (SEQ ID NO:1178), PAFQYSSHVSLQASSGHMWGTFRFER (SEQ ID NO:1179), RLPCHKRRRCFCLVIQKKSFKFEMLDGNLISGGVGEDVFMADIVQAWDGIIEGP
 30 TVIMVSQEGHSFCLRLSLRYMWAVTSINQHLIVSVSFAFHLLGAMASRVLCFF WSCRSHIPVXQSGLPKGQDDTSVAKNAMKEKLPGLIFSILFWHLKHTNCLQH FALWSVSGREVPVRRRGRRWREGSSXGRAQSGLGHRAXVSDRDHQRLPTAR

PPGCTGCHVPPERRPAADTEPNP (SEQ ID NO:1180),
KEFMLDGNLISGGVGEDVFMADIVQAWDGIE (SEQ ID NO:1181),
AVTSINQHLIVSVSFAFHLLGAMASRVLC (SEQ ID NO:1182), and/or
TARPPGCTGCHVPPERRPAA (SEQ ID NO:1183). Moreover, fragments and
5 variants of these polypeptides (such as, for example, fragments as described herein,
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to
these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,
under stringent conditions, to the polynucleotide encoding these polypeptides) are
encompassed by the invention. Antibodies that bind polypeptides of the invention are
10 also encompassed by the invention. Polynucleotides encoding these polypeptides are
also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome
17. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 17.

15 This gene is expressed primarily in gall bladder, prostate, and fetal brain, and
to a lesser extent, in tumor and fetal tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for
differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include, but are not limited to,
20 gastrointestinal, reproductive, neural, or growth related disorders such as cancers.
Similarly, polypeptides and antibodies directed to these polypeptides are useful in
providing immunological probes for differential identification of the tissue(s) or cell
type(s). For a number of disorders of the above tissues or cells, particularly of the
prostate, gall bladder, and fetal brain, expression of this gene at significantly higher or
25 lower levels may be routinely detected in certain tissues or cell types (e.g.,
gastrointestinal, reproductive, neural, developmental, and cancerous and wounded
tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine,
synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
30 the expression level in healthy tissue or bodily fluid from an individual not having the
disorder.

The tissue distribution in fetal brain and tumor tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of growth-related disorders, such as cancers. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival, in addition to metabolic, or reproductive disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:193 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1524 of SEQ ID NO:193, b is an integer of 15 to 1538, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 184

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: SLCCPEGAEGC (SEQ ID NO:1184), QLKKTHYDRPCP (SEQ ID NO:1185), QLKKTHYDRPCP (SEQ ID NO:1186),
5 MNRPCPFCLWKVFPLLLLLHEELFPLPVP (SEQ ID NO:1187), and/or KEKTFTPRNSLCCPEGAEGCIAGGDLQLKKTHY (SEQ ID NO:1188). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
10 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in stromal cell, tonsil, and glioblastoma.

15 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immune and inflammatory disorders, in addition to neural disorders, such as glioblastoma. Similarly, polypeptides and antibodies directed to these
20 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the stromal cells, tonsil, and glioblastoma expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, and cancerous and
25 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Additionally, it is believed that the product of this gene regulates pancreatic cell
30 differentiation into beta cells. Accordingly, polynucleotides and polypeptides of the invention are useful in the treatment of insulin-dependent diabetes mellitus and

associated conditions e.g. pancreatic hypofunction and the prevention, as well as the treatment of undifferentiated type pancreatic cancers.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 432 as residues: Pro-27 to Ala-32.

5 The tissue distribution in stromal cells and tonsils indicates that the protein product of this gene is useful for diagnosis and treatment of immune and inflammatory disorders and glioblastoma. Similarly, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells
10 are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene
15 product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:194 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1084 of SEQ ID NO:194, b is an integer of 15 to 1098, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 185

This gene is expressed primarily in hepatocellular carcinoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic or metabolic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, metabolic, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 433 as residues: Gly-32 to Lys-39.

The tissue distribution in hepatocellular carcinoma tissue indicates that the protein product of this gene is useful for diagnosis and treatment of liver diseases. Moreover, the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the protein may have a useful role in treating, detecting, or preventing developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:195 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 987 of SEQ ID NO:195, b is an integer of 15 to 1001, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 186

10 This gene is expressed primarily in hippocampus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neuronal or endocrine disorders, particularly behavioral and mood disorders.

15 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hippocampus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, endocrine, and
20 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 434 as residues: Ser-14 to Tyr-20.

The tissue distribution in hippocampus indicates that the protein product of this gene is useful for the diagnosis and treatment of neuronal disorders. Moreover, the protein product of this gene is useful for the detection/treatment of
30 neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating

diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:196 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1444 of SEQ ID NO:196, b is an integer of 15 to 1458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 187

This gene is expressed primarily in bone cancer and hippocampus, and to a lesser extent, in osteoclastoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, bone-related disorders and neuronal diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone, osteoclast, and hippocampus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in hippocampus and skeletal tissues indicates that the protein product of this gene is useful for diagnosis and treatment of bone-related disorders and neuronal diseases. Similarly, this gene product is useful in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Alternatively, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:197 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:197, b is an

integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 188

The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

10 This gene is expressed primarily in neuronal tissues such as hippocampus, spinal cord, and hypothalamus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, 15 neuronal diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell 20 types (e.g. neuronal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in neuronal tissues indicates that the protein product of this gene is useful for diagnosis and treatment of neuronal disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, 30 including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked

disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:198 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 937 of SEQ ID NO:198, b is an integer of 15 to 951, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 189**

The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

20 This gene is expressed primarily in neuronal tissues and immune tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neuronal and immune-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal and immune-related tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. neuronal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 437 as residues: Pro-19 to Asp-25.

5 The tissue distribution neuronal and immune tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of neuronal and immune-related disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, neuronal disorders, and behavioral disorders such as Alzheimer's
10 Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of
15 developmental disorders associated with the developing embryo, or sexually-linked disorders. Additionally, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as,
20 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial
25 utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:199 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1726 of SEQ ID NO:199, b is an
 5 integer of 15 to 1740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 190

10

The translation product of this gene shares sequence homology with human N33, a gene located in a homozygously deleted region of human metastatic prostate cancer, which is thought to be important in prevention of prostate cancer. The gene and its translation product also share sequence homology with an isolated
 15 prostate/colon tumor suppressor gene (PSTG) product (WO9532214-A1.).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

AQRKKEMVLSEKVSQLEWTKRPMNGDKFRRLVKAPPRNYSVIVMFT
 ALQLHRQCVVCKQADEEFQILANSWRYSSAFTNRIFAMVDFDEGSDVFQML

20 NMNSAPTFINFPAGKPKRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPP
 NMAARWRFWCVSVT (SEQ ID NO:1189), MVVALLIVCDVPSAS (SEQ ID
 NO:1190), AQRKKEMVLSEKVSQLEWTKRPMNGDKFRRLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRYSSAFTNR
 MEWTKRPMNGDKFRRLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRYSSAFTNR
 25 IFFA (SEQ ID NO:1193), MVDFDEGSDVFQMLNMNSAPTFINFPAGKPK (SEQ
 ID NO:1194), KRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPPN (SEQ ID
 NO:1195), and/or

YAGPLMLGLLLAVIGGLVYLRRVIWNFSLIKLDGLLQLCVLCLL (SEQ ID

30 NO:1196). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in infant adrenal gland, prostate cell line, and to a lesser extent in adrenal gland.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer and endocrine disorders. Similarly, polypeptides and antibodies
10 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate and adrenal gland, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, endocrine, cancerous and wounded tissues) or
15 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
20 NO: 438 as residues: Pro-34 to Gly-43, Arg-113 to Pro-120.

The tissue distribution infant adrenal gland, combined with the homology to N33 and prostate/colon tumor suppressor gene (PSTG) indicates that the protein product of this gene is useful for the diagnosis and treatment for prostate cancer and endocrine disorders, and that the nucleic acids and proteins of this gene can be used in
25 the diagnosis and treatment of prostate, endocrine and colorectal cancers. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
30 related to SEQ ID NO:200 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1693 of SEQ ID NO:200, b is an integer of 15 to 1707, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 191

This gene is expressed primarily in T-cell, and to a lesser extent in fetal lung. Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and respiratory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, respiratory, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 439 as residues: Trp-3 to Phe-9.

The tissue distribution in T-cells and fetal lung indicates that the protein product of this gene is useful for the diagnosis and treatment of immune and respiratory disorders. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor

marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. The tissue distribution also indicates that the protein product of this gene is useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:201 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 765 of SEQ ID NO:201, b is an integer of 15 to 779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 192

The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in

linkage analysis for chromosome 6. The translation product of this gene shares significant homology with the rat protein Neuritin, and in fact appears to be a human ortholog of the rat protein. It is believed that this gene is induced in rats by neural activity and neurotrophins, and that it promotes neuritogenesis. Neural activity and neurotrophins induce synaptic remodeling in part by altering gene expression. This gene is believed to be a glycosylphosphatidylinositol-anchored protein encoded by a hippocampal gene, and to possess neural activity. This molecule is believed to be expressed in post-mitotic differentiating neurons of the developing nervous system and neuronal structures associated with plasticity in the adult. Message of this gene is believed to be induced by neuronal activity and by the activity-regulated neurotrophins BDNF and NT-3. The product of this gene is believed to stimulate neurite outgrowth and arborization in primary embryonic hippocampal and cortical cultures, and to act as a downstream effector of activity-induced neurite outgrowth. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: DAVFKGFSDCLLKLGD (SEQ ID NO:1197), CQEGAKDMWDKLRKESKNLN (SEQ ID NO:1198), VLLVSLAALATWLSF (SEQ ID NO:1199), MGLKLNGRYISLILAVQIAYLVQAVRAAGKCD VFKGFSDCLLKLGD (SEQ ID NO:1200), PAAWDDKTNIKTVCTYWEDFHSCVTALTDCQEGAKDMWDKLRKESKNLN IQGSLFELCGSGNGAAGSLLPAFPVLLVSLAALATWLSF (SEQ ID NO:1201), and/or MGLKLNGRYISLILAVQIAYLVQAVRAAGKCD VFKGFSDCLLKLGD XXXX XX PAAWDDKTNIKTVCTYWEDFHSCVTALTDCQEGAKDMWDKLRKESKN LNIQGSLFELCGSGNGAAGSLLPAFPVLLVSLAALATWLSF (SEQ ID NO:1202). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human placenta, endometrial tumor and tissues of the central nervous system (CNS).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to reproductive disorders, cancers and neurological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and neurological disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, neurological, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 440 as residues: Asp-47 to Asp-63, His-75 to Tyr-80, Pro-83 to Tyr-89.

The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and treatment of reproductive disorders such as endometrial tumors. Expression of this gene in tissues of the CNS, and its strong homology to Neuritin, suggest that the protein product from this gene is also useful in the treatment and diagnosis of neurological disorders and in the regeneration of neural tissues, e.g., following injury.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:202 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1603 of SEQ ID NO:202, b is an

integer of 15 to 1617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 193

The translation product of this gene shares sequence homology with tenascin, which is thought to be important in development. The translation product of this gene is believed to be a ligand of the fibroblast growth factor family. FGF ligand activity is known in the art and can be assayed by methods known in the art and disclosed elsewhere herein.

Northern analysis indicates that a 2.5 kb band is expressed in brain and lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, growth disorders of the brain and lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer tissues, brain, lung, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, lung, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 441 as residues: Gly-29 to Glu-34, Arg-71 to Arg-76, Thr-176 to Cys-182, Gly-184 to Glu-199.

The tissue distribution in brain and lung, combined with the homology to tenascin indicates that the protein product of this gene is useful for diagnosis and treatment of cancers. Alternatively, given the tissue distribution indicated by Northern analysis, the translation product of this gene is thought to be a growth factor

functioning in the brain and lung that may be useful in treating neurodegeneration and lung disorder. For example, the protein product of this gene is useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. Furthermore, the tissue
5 distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division. Additionally, expression in the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It
10 may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:203 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1960 of SEQ ID NO:203, b is an integer of 15 to 1974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 194

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
30 MNSAAGFSHLDRRERVLKLGESFEKQPRCASTLC (SEQ ID NO:1203). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,

97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides
5 encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal human lung and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
10 lung development and respiratory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain
15 tissues or cell types (e.g. respiratory, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 The tissue distribution in fetal lung and neutrophils indicates that the protein product of this gene is useful for the diagnosis and treatment of lung and immunity related diseases, for example, lung cancer, viral, fungal or bacterial infections (e.g. lesions caused by tuberculosis), inflammation (e.g. pneumonia), metabolic lesions etc. Furthermore, the tissue distribution indicates that the protein product of this gene
25 is useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Protein, as
30 well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:204 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1043 of SEQ ID NO:204, b is an integer of 15 to 1057, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 195

This gene is expressed primarily in breast lymph node, and to a lesser extent in synovial tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and skeletal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast lymph node and synovium indicates that the protein product of this gene is useful for the diagnosis and treatment of immune and skeletal disorders. Furthermore, this gene product may be involved in the regulation

of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The expression of this gene product in synovium indicates a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:205 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 707 of SEQ ID NO:205, b is an

integer of 15 to 721, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 196

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5. The translation product of this gene shares

10 sequence homology with human M-phase phosphoprotein 4, which is thought to be important in the phosphorylation and signal transduction processes.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

TIYPTEEELQAVQKIVSITERALKLVSD (SEQ ID NO:1204),

15 RALKGVLRVGVLAKEGLLLRGDRNVNLVLLC (SEQ ID NO:1205),

ALAALRHAKWFQARANGLQSCVIIIIRLDLCQRVPTWS (SEQ ID NO:1206),

GDALRRVFECISSGIL (SEQ ID NO:1207), LAFRQIHKVLGMDPLP (SEQ ID NO:1208),

and/or

TIYPTEEELQAVQKIVSITERALKLVSDSLSEHEKNKNKEGDDKKEGGKDRAL

20 KGVLRVGVLAKEGLLLRGDRNVNLVLLCSEKPSKTLLSRIAENLPKQLAVISPE

KYDIKCAVSEAAIILNSCVEPKMQVTITLTSPITREENMREGDVTSGMVKDPPD

VLDRQKCLDALAALRHAKWFQARANGLQSCVIIIIRLDLCQRVPTWSDFPS

WAMELLVEKAISSASSPQSPGDALRRVFECISSGILKGSPGLLDPCFKDPFDL

ATMTDQQREDITSSAQFALRLLAFRQIHKVLGMDPLPQMSQRFNIHNNRKR

25 RDSGDVDGFEEAGKKDKKDYDNF (SEQ ID NO:1209), MERHPKKKMCSD

(SEQ ID NO:1210), and/or GENSSSDFPLFLFYFLVALASPPIFVSFIN (SEQ ID NO:1211). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by

30 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind

polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human hippocampus, and to a lesser extent in prostate and human frontal cortex.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders related to the reproductive and nervous systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
10 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial
15 fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID
NO: 444 as residues: Arg-13 to Asp-21, Lys-28 to Lys-38, Val-76 to Asp-81, Ser-99
20 to Ala-107, Pro-130 to Phe-136, Thr-143 to Ile-150, Pro-176 to Phe-182, Asn-186 to Gly-196, Ala-202 to Phe-214.

The tissue distribution in human hippocampus, prostate, and frontal cortex, combined with the homology to human M-phase phosphoprotein 4 indicates that the protein product of this gene is useful for the diagnosis and treatment of reproductive
25 and nervous system disorders. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS;
30 or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:206 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2451 of SEQ ID NO:206, b is an integer of 15 to 2465, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 197

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: MGSQHSAAARPSSCRRKQEDDRDG (SEQ ID NO:1212), LLAEREQEEAIAQFPYVEFTGRDSITCLTC (SEQ ID NO:1213), and/or QGTGYIPTEQVNELVALI PHSDQRLRPQRTKQYV (SEQ ID NO:1214). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human primary breast cancer, and to a lesser extent, in human adult spleen, Hodgkin's lymphoma I, and salivary gland.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, as well as immune disorders. Similarly, polypeptides and antibodies directed

to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly cancers and the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 445 as residues: Ser-126 to Gly-138.

The tissue distribution in tumors of breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Furthermore, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:207 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1466 of SEQ ID NO:207, b is an integer of 15 to 1480, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 198

This gene is expressed primarily in monocytes.

- 5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, blood cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
- 10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
- 15 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution in monocytes indicates that the protein product of this gene is useful for the diagnosis and treatment of blood cell disorders. Furthermore,
- 20 expression of this gene product in monocytes also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly
- 25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:208 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
- 30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:208, b is an

integer of 15 to 872, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 199

The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

10 This gene is expressed primarily in human ovary and synovia, and to a lesser extent in human 8 week whole embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive and developmental disorders. Similarly, polypeptides and antibodies
15 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and developmental systems, expression of this gene at significantly higher or lower levels may be routinely
20 detected in certain tissues or cell types (e.g. reproductive, developmental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in human ovary and human 8 week whole embryo indicates that the protein product of this gene is useful for the diagnosis and treatment of reproductive and developmental disorders. Similarly, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in
30 the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or

tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:209 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1765 of SEQ ID NO:209, b is an integer of 15 to 1779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 200

The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8. The translation product of this gene shares limited sequence homology with collagen proline rich domain.

This gene is expressed primarily in CNS.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample

taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

5 NO: 448 as residues: Pro-35 to Asp-41.

The tissue distribution in tissues of the central nervous system indicates that the protein product of this gene is useful for the diagnosis and treatment of neurological diseases and disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, 10 paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies 15 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:210 and may have been publicly available prior to conception 20 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2096 of SEQ ID NO:210, b is an 25 integer of 15 to 2110, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 201

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The translation product of this gene shares homology with a mammalian histone H1a protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: ARLNVGRESLKREMLKSQGVKVSSEPMGARHSSWPEGAAFCCKVQGAQMQ FPPRR (SEQ ID NO:1215), ARLNVGRESLKREML (SEQ ID NO:1216), LKSQGV
5 KVSSEPMGARHSSW (SEQ ID NO:1217), AFCKKVQGAQM QFPPRR (SEQ ID NO:1218), and/or AFCKKVQGAQM QFPPRR (SEQ ID NO:1219). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
10 which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. pir|S24178).

15 This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these
20 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph,
25 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this
30 gene is useful for the diagnosis and treatment of immune disorders. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in vital immune functions. Therefore it may be also used as an agent for immunological

disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Protein, as well as, antibodies directed against the protein may show utility as a tumor
5 marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:211 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:211, b is an integer of 15 to 938, where both a and b correspond to the positions of nucleotide
15 residues shown in SEQ ID NO:211, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 202

20 This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these
25 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph,
30 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the diagnosis and treatment of immune disorders. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:212 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1537 of SEQ ID NO:212, b is an integer of 15 to 1551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 203

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infectious disorders, immune disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or
5 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 451 as residues: Thr-31 to Lys-36.

10 The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the diagnosis and treatment of infectious disorders, immune disorders, and cancers. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune
15 deficiency diseases such as AIDS, and leukemia. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:213 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 983 of SEQ ID NO:213, b is an integer of 15 to 997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 204

The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16. The translation product of this gene shares
5 sequence homology with lactate dehydrogenase, which is thought to be important in lactate metabolism.

This gene is expressed primarily in human tonsils, and to a lesser extent, in spleen, and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, infectious disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
15 disorders of the above tissues or cells, particularly of the immune disorders, infectious disorders, and cancers, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. tonsils, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an
20 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 452 as residues: Gly-7 to Ser-12.

25 The tissue distribution in human tonsils, spleen, and neutrophils, combined with the homology to lactate dehydrogenase gene indicates that the protein product of this gene is useful for the diagnosis and treatment of immune disorders, infectious disorders, and cancers. Furthermore, expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or
30 activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of

cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:214 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1482 of SEQ ID NO:214, b is an integer of 15 to 1496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 205

The translation product of this gene shares sequence homology with Gcap1 protein which is developmentally regulated in brain.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
NFFFVCLFKSSLRLVNSSYTPILCVL (SEQ ID NO:1220). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in placenta and endometrial tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vasculogenesis/angiogenesis and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. placental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 453 as residues: Lys-9 to Gln-16.

The tissue distribution placenta and endometrial tumors, combined with the homology to Gcap1 protein indicates that the protein product of this gene is useful for the diagnosis and treatment of disorders or dysfunctions of the vascular system, which include, but are not limited to atherosclerosis, hypertension, embolism, thrombosis, microvascular disease, aneurysm, or stroke, or tumorigenesis. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta

indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of
 5 this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may
 10 serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:215 and may have been publicly available prior to conception
 15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1294 of SEQ ID NO:215, b is an
 20 integer of 15 to 1308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 206

25

The translation product of this gene shares sequence homology with a *C. elegans* protein of unknown function (F23B2.4 [*Caenorhabditis elegans*]).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:
 30 VQVLEQLTNNVAESRFNDAAYYYWMLSMQCLDIAQD (SEQ ID NO:1221),
 PAQKDTMLGKFYHFQRLAELYHGYHAIHRHTEDP (SEQ ID NO:1222),
 LAKQSKALGAYRLARHAYDKLRGLYIP (SEQ ID NO:1223),

ARFQKSIELGTLTIRAKPFHDSEELVPLCYRCSTNN (SEQ ID NO:1224),
PLLNNLGNVCINCRQPFIFSASSYDVLHLVEFYLEEGITDEEAISLIDLEVLRPK
RDDRQLEICKQQLPDSCG (SEQ ID NO:1225)
MPYAQWLAENDRFEEAQKAFHKAGRQREA (SEQ ID NO:1226), and/or
5 FSVHRPETLFNISRFLHSLPKDTPSGISKVKILFT (SEQ ID NO:1227).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
10 encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for
15 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
20 the above tissues or cells, particularly of the reproductive and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a
25 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes indicates that the protein product of this gene is useful for the treatment of male reproductive and endocrine disorders.

Furthermore, the tissue distribution indicates that the protein product of this gene is
30 useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This

gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:216 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1691 of SEQ ID NO:216, b is an integer of 15 to 1705, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 207

This gene is expressed in fetal lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, lung diseases such as cystic fibrosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

types (e.g. respiratory, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
5 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 455 as residues: Tyr-49 to Cys-54.

The tissue distribution in fetal lung indicates that the protein product of this gene is useful for the detection and treatment of disorders associated with developing
10 lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker
15 and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:217 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 985 of SEQ ID NO:217, b is an integer of 15 to 999, where both a and b correspond to the positions of nucleotide
25 residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.

Table 1

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HLHDS67	97979 03/27/97	Uni-ZAP XR	11	2526	427	2526	458	458	249	1	30	31	30
2	HLHDZ58	97979 03/27/97	Uni-ZAP XR	12	1131	1	1131	129	129	250	1	14	15	115
3	HLMMJ13	97979 03/27/97	Lambda ZAP II	13	941	39	941	62	62	251	1	44	45	102
3	HLMMJ13	97979 03/27/97	Lambda ZAP II	218	941	39	941	245	245	456	1	35	36	41
4	HLTEI25	97979 03/27/97	Uni-ZAP XR	14	843	1	843	155	155	252	1	19	20	42
5	HMSJX24	97979 03/27/97	Uni-ZAP XR	15	1018	1	1018	90	90	253	1	18	19	36
6	HNFE65	97979 03/27/97	Uni-ZAP XR	16	661	1	661	76	76	254	1	28	29	127
7	HNHDX07	97979 03/27/97	Uni-ZAP XR	17	553	1	553	106	106	255	1	23	24	66
8	HNHGC82	97979 03/27/97	Uni-ZAP XR	18	869	1	869	101	101	256	1	21	22	68

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
9	HNHGO09	97979 03/27/97	Uni-ZAP XR	19	959	1	959	176	176	257	1	21	22	43
10	HOUBE18	97979 03/27/97	Uni-ZAP XR	20	1446	1	1446	101	101	258	1	27	28	50
11	HOUDL69	97979 03/27/97	Uni-ZAP XR	21	1471	579	1460	692	692	259	1	31	32	42
12	HPMFI71	97979 03/27/97	Uni-ZAP XR	22	1402	242	1402	401	401	260	1	32	33	60
13	HPMGQ55	97979 03/27/97	Uni-ZAP XR	23	1047	1	1047	164	164	261	1	26	27	35
14	HPQAC69	97979 03/27/97	Lambda ZAP II	24	990	1	988	82	82	262	1	20	21	37
15	HPTBB03	97979 03/27/97	Uni-ZAP XR	25	1208	350	1173	398	398	263	1	29	30	210
16	HPTWA66	97979 03/27/97	pBluescript	26	1922	1381	1922	24	24	264	1	33	34	547
16	HPTWA66	97979 03/27/97	pBluescript	219	575	1	575	148	148	457	1	22	23	65
17	HPTWC08	97979 03/27/97	pBluescript	27	1951	1422	1874	219	219	265	1	19	20	299
18	HRGCZ46	97979 03/27/97	Uni-ZAP XR	28	3989	2635	3989			266	1	16	17	39

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
19	HSAVU34	97979 03/27/97	Uni-ZAP XR	29	3735	2966	3735	272	272	267	1	30	31	594
19	HSAVU34	97979 03/27/97	Uni-ZAP XR	220	3018	1929	3018	26	26	458	1	1	2	156
20	HSDFW61	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	30	1667	59	1625	138	138	268	1	32	33	130
21	HSDGP60	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	31	1408	1	1408	285	285	269	1			20
22	HSOAJ55	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	32	3186	2402	3186	302	302	270	1	43	44	159
22	HSOAJ55	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	221	2031	1273	2031	1285	1285	459	1	29	30	30

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
23	HSQEO84	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	33	971	13	971	91	91	271	1	19	20	218
23	HSQEO84	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	222	968	8	968	86	86	460	1	20	21	56
24	HSXAM05	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	34	1792	369	1792	470	470	272	1	26	27	49
25	HSXAS67	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	35	896	1	896	96	96	273	1	32	33	121
26	HTDAF28	97974 04/04/97 209080 05/29/97	pSport1	36	912	1	912	38	38	274	1	22	23	87

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
27	HTEGQ64	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	37	1382	67	1382	271	275	1			25
28	HTGEU09	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	38	872	1	872	74	276	1	18	19	28
29	HTOAM21	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	39	812	1	812	41	277	1	30	31	43
30	HTPBW79	209511 12/03/97	Uni-ZAP XR	40	1515	118	1507	302	278	1	24	25	362
30	HTSEV09	97974 04/04/97 209080 05/29/97	pBluescript	223	1404	1	1265	92	461	1	19	20	415
31	HJPCD40	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	41	704	22	704	117	279	1	18	19	127

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
32	HTWBY48	97974 04/04/97 209080 05/29/97	pSport1	42	1094	1	1094	32	32	280	1	34	35	53
33	HTWCI46	97974 04/04/97 209080 05/29/97	pSport1	43	1821	892	1647	56	56	281	1	26	27	29
34	HTXGI75	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	44	1024	30	1024		167	282	1	20	21	25
35	HWTBF59	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	45	983	779	983	85	85	283	1	30	31	221
35	HWTBF59	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	224	707	488	707	514	514	462	1	41	42	64

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
36	HADAE74	97974 04/04/97 209080 05/29/97	pSport1	46	2421	664	1587	2110	2110	284	1	33	34	40
37	HAGFB60	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	47	840	1	840	97	97	285	1	30	31	48
38	HATEF60	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	48	2432	1193	2246	1491	1491	286	1	17	18	51
39	HBMSN25	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	49	1742	1165	1742	1207	1207	287	1	23	24	31
40	HCDAR68	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	50	1487	181	1455	325	325	288	1	35	36	56

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
41	HCE3J79	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	51	1328	251	1328	525	525	289	1			21
42	HMDAN54	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	52	1856	725	1853	928	928	290	1	33	34	50
43	HCECA49	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	53	1558	310	1408	109	109	291	1	30	31	98
44	HCEEC15	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	54	948	1	948	9	9	292	1	23	24	65
45	HCESF40	97974 04/04/97 209080 05/29/97	pBluescript	55	990	99	990	193	193	293	1	32	33	256

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
45	HCESF40	97974 04/04/97 209080 05/29/97	pBluescript	225	1384	99	1384	193	193	463	1	32	33	205
46	HCFMV39	97974 04/04/97 209080 05/29/97	pSport1	56	1603	1	1296	96	96	294	1	29	30	102
47	HCMSX86	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	57	1052	5	786	12	12	295	1	28	29	32
48	HCNAP62	97975 04/04/97 209081 05/29/97	Lambda ZAP II	58	814	1	558	93	93	296	1	22	23	42
49	HCRAF32	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	59	1215	257	1215		356	297	1	19	20	20

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	NT Total Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
50	HCUDC07	97975 04/04/97 209081 05/29/97	ZAP Express	60	478	1	478	147	147	298	1	36	37	69
51	HCWBB42	97975 04/04/97 209081 05/29/97	ZAP Express	61	618	1	618	212	212	299	1	35	36	74
52	HDTAB05	97975 04/04/97 209081 05/29/97	pCMVSPORT 2.0	62	751	1	751	257	257	300	1	21	22	32
53	HE2AV74	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	63	780	283	780		433	301	1			16
54	HE2AY71	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	64	588	21	588	169	169	302	1			16

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
55	HE2GS36	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	65	945	1	349	520	520	303	1	39	40	111
55	HE2GS36	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	226	774	272	774	445	445	464	1			37
56	HE2OF09	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	66	1866	1313	1866	1596	1596	304	1			11
57	HE6EU50	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	67	1152	117	686	237	237	305	1	20	21	34
58	HE9HU17	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	68	2483	1577	2448	1620	1620	306	1			14

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
59	HE9ND48	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	69	536	1	536	83	83	307	1	36	37	43
60	HEBBW11	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	70	574	97	564	109	109	308	1	55	56	137
60	HEBBW11	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	227	865	647	865		388	465	1	30	31	135
61	HELDY74	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	71	932	1	932	201	201	309	1	17	18	33
62	HEMAE80	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	72	996	1	945	12	12	310	1	24	25	136

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT 3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
63	HFEB88	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	73	785	464 785	356	356	311	1	29	30	57
64	HFGAB89	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	74	1069	196 1047	295	295	312	1	32	33	34
65	HFVHY45	97975 04/04/97 209081 05/29/97	pBluescript	75	831	1 831	50	50	313	1	36	37	89
66	HGBAJ93	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	76	590	1 590	233	233	314	1	38	39	94
67	HGBBQ69	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	77	1274	1 1273	105	105	315	1	24	25	43

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
68	HHFCF08	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	78	1133	4	1042	175	175	316	1	23	24	30
69	HHFHJ59	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	79	661	1	661	192	192	317	1	29	30	112
70	HHFHR32	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	80	1378	1	1378	58	58	318	1	25	26	235
71	HHGCN69	97975 04/04/97 209081 05/29/97	Lambda ZAP II	81	1440	298	1440	532	532	319	1	23	24	34
72	HHGDO13	97975 04/04/97 209081 05/29/97	Lambda ZAP II	82	1381	766	1371	993	993	320	1	23	24	34

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
73	HHPFD63	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	83	1706	182	1644	257	257	321	1	24	25	81
74	HHSEG23	97976 04/04/97	Uni-ZAP XR	84	573	1	573	160	160	322	1	18	19	71
75	HJPAV06	97976 04/04/97	Uni-ZAP XR	85	684	199	684	323	323	323	1	27	28	33
76	HKIXL73	97976 04/04/97	pBluescript	86	1036	591	1036	690	690	324	1	32	33	114
77	HKMNC43	97976 04/04/97	pBluescript	87	908	1	908	139	139	325	1	18	19	108
78	HMEJE31	97976 04/04/97	Lambda ZAP II	88	655	1	655	165	165	326	1	33	34	64
79	HMSKS35	97976 04/04/97	Uni-ZAP XR	89	1102	1	1102	228	228	327	1	23	24	49
79	HMSKS35	97976 04/04/97	Uni-ZAP XR	228	1102	1	1102	228	228	466	1	26	27	49
80	HNF AE54	97976 04/04/97	Uni-ZAP XR	90	1533	665	1518	347	347	328	1	26	27	293
81	HNFJH45	97976 04/04/97	Uni-ZAP XR	91	575	1	575	275	275	329	1	30	31	67

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
82	HNGBT31	97976 04/04/97	Uni-ZAP XR	92	639	1	639	224	224	330	1	28	29	104
83	HNGIN60	97976 04/04/97	Uni-ZAP XR	93	858	1	858	239	239	331	1	23	24	58
83	HNGIN60	97976 04/04/97	Uni-ZAP XR	229	744	1	744	225	225	467	1	43	44	70
84	HNGIG84	97976 04/04/97	Uni-ZAP XR	94	526	1	526	268	268	332	1	29	30	38
85	HNHDW42	97976 04/04/97	Uni-ZAP XR	95	426	1	426	168	168	333	1	28	29	71
86	HNHFL57	97976 04/04/97	Uni-ZAP XR	96	844	1	844	98	98	334	1	25	26	61
87	HOGAR52	97977 04/04/97 209082 05/29/97	pCMVSPORT 2.0	97	1985	453	1985	533	533	335	1	17	18	285
88	HOSBZ55	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	98	1416	69	1416	246	246	336	1	32	33	54

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
89	HOSDI92	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	99	1760	1469	1760	934	934	337	1	22	23	59
89	HOSDI92	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	230	1935	141	772		274	468	1	20	21	58
90	HPBCU51	97977 04/04/97 209082 05/29/97	pBluescript SK-	100	599	1	599	86	86	338	1	27	28	119
91	HPCAL49	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	101	784	1	784	113	113	339	1	36	37	38
92	HPFCR13	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	102	404	1	404	266	266	340	1	30	31	46

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	Signal AA of First AA of NT	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
92	HPFCR13	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	231	1035	602	1035	859	859	469	1	32	33	58
93	HPHAC83	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	103	2218	840	2182	1035	1035	341	1	17	18	17
93	HOFNZ45	209568 01/06/98	pCMVSPORT 2.0	232	760	1	728	86	86	470	1	36	37	61
94	HPMBQ32	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	104	1351	1	1351	18	18	342	1	23	24	86
95	HPWAN23	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	105	2066	51	2052	270	270	343	1	29	30	537
95	HPWAN23	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	233	2057	1	1954	220	220	471	1	29	30	315

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
96	HRDFB85	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	106	1705	23	1697	233	344	1	21	22	201
97	HRGBR28	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	107	1167	1	557	604	345	1	22	23	122
98	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	108	1907	151	1432	353	346	1	23	24	260
98	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	234	2084	335	2084	537	472	1	19	20	23
99	HSPAH56	97977 04/04/97 209082 05/29/97	pSport1	109	611	1	576	229	347	1	25	26	47
100	HE8EU04	209746 04/07/98	Uni-ZAP XR	110	2632	294	2632	337	348	1	25	26	333

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
100	HSXBT86	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	235	2143	53	1096	235	235	473	1			9
101	HSXCS62	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	111	2249	1	1953	90	90	349	1	18	19	199
102	HTEFU09	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	112	2198	228	2158	400	400	350	1			23
103	HTEKM35	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	113	1043	40	1043	320	320	351	1	20	21	142
104	HTGEP89	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	114	703	1	703	285	285	352	1	29	30	94

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
105	HTGEW91	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	115	3684	526	1338	584	584	353	1	24	25	37
106	HTOEY16	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	116	1965	127	1915	202	202	354	1	27	28	38
107	HTPCN79	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	117	503	1	503		1	355	1	7	8	70
108	HTSGM54	97977 04/04/97 209082 05/29/97	pBluescript	118	1071	50	981	29	29	356	1	30	31	227
108	HTSGM54	97977 04/04/97 209082 05/29/97	pBluescript	236	1133	316	1069		423	474	1	12	13	84

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
109	HTSHE40	97977 04/04/97 209082 05/29/97	pBluescript	119	1101	118	956	218	218	357	1	31	32	89
110	HTWAF58	97977 04/04/97 209082 05/29/97	Lambda ZAP II	120	282	1	282	137	137	358	1	25	26	48
111	HTWBY29	97977 04/04/97 209082 05/29/97	pSport1	121	2635	1593	2489	1654	1654	359	1	25	26	55
112	HUKFC71	209007 04/28/97 209083 05/29/97	Lambda ZAP II	122	994	1	932		272	360	1	15	16	221
113	HCE3Q10	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	123	1542	1	1542	143	143	361	1	25	26	63

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
114	HCEVR60	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	124	1390	82	1390	127	127	362	1	32	33	153
115	HDTAW95	209007 04/28/97 209083 05/29/97	pCMVSPORT 2.0	125	1288	412	1288	571	571	363	1			16
116	HE6EL90	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	126	1517	1	1452	243	243	364	1			9
117	HELBU29	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	127	1073	198	1073		776	365	1			13
118	HERAH36	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	128	300	155	300	202	202	366	1			17

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
119	HFXBW82	209007 04/28/97 209083 05/29/97	Lambda ZAP II	129	1275	1	1275	56	56	367	1	23	24	61
120	HHPTD20	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	130	472	51	472		243	368	1			32
121	HIBED17	209007 04/28/97 209083 05/29/97	Other	131	1950	284	1927	395	395	369	1	72	73	245
122	HLTER03	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	132	990	1	990	78	78	370	1	22	23	34
123	HOABL56	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	133	1720	565	1720	660	660	371	1	18	19	21

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
124	HPMCJ92	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	134	705	28	705	106	106	372	1	28	29	98
125	HPWAZ95	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	135	323	1	323	88	88	373	1	27	28	78
126	HRGBR18	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	136	582	1	582		16	374	1	17	18	30
127	HSUBW09	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	137	1021	1	1021	153	153	375	1	32	33	56
128	HUKCO64	209007 04/28/97 209083 05/29/97	Lambda ZAP II	138	1777	1	1339	198	198	376	1	23	24	63

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
129	H6EAA53	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	139	643	303	643	306	306	377	1	14	15	38
130	HAGAI11	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	140	1220	1	1220	567	567	378	1	50	51	98
131	HAGAO39	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	141	721	1	721		415	379	1			14
132	HALSK07	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	142	1468	125	1468	210	210	380	1	29	30	33
133	HALSQ59	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	143	300	4	300	101	101	381	1	22	23	66
134	HAIBP89	209877 05/18/98	Uni-ZAP XR	144	2243	173	2243	311	311	382	1	27	28	317

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
134	HBGCB91	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	237	1025	409	1025	624	624	475	1	20	21	25
135	HBMTD81	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	145	1082	163	1082	357	357	383	1			30
136	HBXGK12	209008 04/28/97 209084 05/29/97	ZAP Express	146	4313	1153	4313	1313	1313	384	1	18	19	42
137	HFKFJ07	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	147	1183	1	1183	149	149	385	1	41	42	254
138	HCQAI40	209008 04/28/97 209084 05/29/97	Lambda ZAP II	148	734	1	734	285	285	386	1			19

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT 3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
139	HCWHZ24	209008 04/28/97 209084 05/29/97	ZAP Express	149	1405	1	1405	108	387	1	34	35	63
140	HE2GT20	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	150	2890	1178	2890	1178	388	1	31	32	39
141	HE8EY43	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	151	2399	1181	2399	1265	389	1	30	31	34
142	HFCEB37	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	152	802	352	802	487	390	1			10
143	HFTCT67	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	153	461	24	461	145	391	1	37	38	63

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
144	HGLAM46	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	154	2388	818	2388	648	392	1			18
145	HHGBR15	209008 04/28/97 209084 05/29/97	Lambda ZAP II	155	642	322	642	369	393	1	41	42	43
146	HJAAU36	209008 04/28/97 209084 05/29/97	pBluescript SK-	156	1251	583	1251	933	394	1	16	17	16
147	HUSIT49	209008 04/28/97 209084 05/29/97	pSport1	157	2127	247	2127	383	395	1	47	48	83
148	HKLAB16	209008 04/28/97 209084 05/29/97	Lambda ZAP II	158	1625	817	1625	1012	396	1	18	19	20

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
149	HLMU76	209008 04/28/97 209084 05/29/97	Lambda ZAP II	159	1687	1307	1687	1296	1296	397	1	28	29	28
150	HMSKQ35	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	160	1842	172	1463	319	319	398	1	30	31	33
151	HNHED86	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	161	770	1	770	30	30	399	1	31	32	46
152	HNHEJ88	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	162	519	1	519	242	242	400	1	17	18	24
153	HNHFQ63	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	163	753	1	753	164	164	401	1	17	18	67
154	HOECU83	209009 04/28/97	Uni-ZAP XR	164	1893	1	1211	1637	1637	402	1	28	29	85

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
154	HOECU83	209009 04/28/97	Uni-ZAP XR	238	1400	189	1400		508	476	1	22	23	33
155	HPTRC15	209009 04/28/97	pBluescript	165	2153	594	2153	57	57	403	1	26	27	82
156	HSKCP69	209009 04/28/97	Uni-ZAP XR	166	1251	219	1120	49	49	404	1	27	28	286
156	HSKCP69	209009 04/28/97	Uni-ZAP XR	239	1250	223	1250	393	393	477	1	32	33	171
157	H6EAE26	209009 04/28/97	Uni-ZAP XR	167	882	48	882	155	155	405	1	33	34	153
158	HAGBX03	209009 04/28/97	Uni-ZAP XR	168	1208	1	1208	290	290	406	1	20	21	37
159	HAGDQ47	209009 04/28/97	Uni-ZAP XR	169	1258	1	1258	44	44	407	1	22	23	60
159	HAGDQ47	209009 04/28/97	Uni-ZAP XR	240	1307	1	1307	44	44	478	1	22	23	60
160	HAICP19	209009 04/28/97	Uni-ZAP XR	170	1624	89	1483	128	128	408	1	18	19	446
161	HAUAE83	209009 04/28/97	Uni-ZAP XR	171	2003	889	2003	957	957	409	1	29	30	64
162	HBHAD12	209009 04/28/97	Uni-ZAP XR	172	786	1	786		176	410	1	17	18	23

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
163	HBM TY28	209009 04/28/97	Uni-ZAP XR	173	1758	962	1758	1184	1184	411	1	27	28	34
164	HBM VP04	209009 04/28/97	Uni-ZAP XR	174	1369	29	557	947	947	412	1	33	34	41
164	HBM VP04	209009 04/28/97	Uni-ZAP XR	241	888	330	862		546	479	1			2
165	HCDD B78	209009 04/28/97	Uni-ZAP XR	175	2379	750	2379	901	901	413	1	18	19	24
166	HCEQA68	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	176	1348	1	1348	12	12	414	1	28	29	78
167	HCEZS40	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	177	1502	178	1502	388	388	415	1	31	32	51
168	HCFNF11	209010 04/28/97 209085 05/29/97	pSport1	178	1637	26	1607	152	152	416	1	44	45	257

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
169	HCRBL20	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	179	2911	1103	2858	192	192	417	1	32	33	424
169	HCRBL20	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	242	1811	20	1811	93	93	480	1	36	37	95
170	HCUBL62	209010 04/28/97 209085 05/29/97	ZAP Express	180	519	1	519	57	57	418	1	28	29	32
171	HDSAP81	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	181	968	320	968	476	476	419	1	27	28	79
172	HE2CT29	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	182	1128	1	1128	111	111	420	1	26	27	94

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT 3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
173	HE8MG65	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	183	2276	48	88	88	421	1	37	38	257
173	HE8MG65	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	243	2271	56	79	79	481	1	43	44	170
174	HE9FB42	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	184	3374	86	277	277	422	1	40	41	704
174	HE9FB42	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	244	2500	76	518	518	482	1	1	2	623
175	HEMAM41	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	185	1337	60	175	175	423	1	39	40	190

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	NT Total Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
175	HEMAM41	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	245	1338	33	1327	175	175	483	1	32	33	91
176	HEMCV19	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	186	941	33	931	79	79	424	1	23	24	178
177	HEMDX17	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	187	678	1	678	131	131	425	1	21	22	40
177	HEMDX17	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	246	654	1	654	137	137	484	1			12
178	HETAR54	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	188	1848	454	1848	948	948	426	1	14	15	232

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of First AA of Signal	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
179	HETBX14	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	189	1292	303	1292	207	427	1	18	19	250
179	HETBX14	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	247	1146	157	1146	74	485	1	14	15	53
180	HFGAB48	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	190	906	156	906	628	428	1	23	24	58
181	HFKFI40	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	191	1941	120	1002	213	429	1	18	19	218
182	HFXHN68	209010 04/28/97 209085 05/29/97	Lambda ZAP II	192	2118	777	2118	966	430	1	23	24	50
183	HGBFO79	209011 04/28/97	Uni-ZAP XR	193	1538	259	1538	273	431	1	23	24	49

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT 3' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
184	HGLAM56	209011 04/28/97	Uni-ZAP XR	194	1098	68	1098	185	432	1	28	29	69
185	HHLBA89	209011 04/28/97	pBluescript SK-	195	1001	1	1001	324	433	1	25	26	39
186	HHPDW05	209011 04/28/97	Uni-ZAP XR	196	1458	1	1458	254	434	1	17	18	104
186	HHPDW05	209011 04/28/97	Uni-ZAP XR	248	1443	1	1443	246	486	1	21	22	21
187	HHPSD37	209011 04/28/97	pBluescript	197	1282	66	1282	171	435	1	19	20	37
188	HHPSF70	209011 04/28/97	pBluescript	198	951	26	951	162	436	1	16	17	34
189	HHSK25	209011 04/28/97	Uni-ZAP XR	199	1740	1390	1740	1534	437	1	19	20	31
190	HLASB53	209011 04/28/97	pBluescript	200	1707	401	1195	652	438	1	26	27	126
191	HLABZ65	209011 04/28/97	pBluescript SK-	201	779	1	779	23	439	1	26	27	68
192	HJPBB39	209011 04/28/97	Uni-ZAP XR	202	1617	188	1605	182	440	1	28	29	91
193	HLHSK94	209011 04/28/97	pBluescript	203	1974	1	1794	112	441	1	26	27	379

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
194	HLHTC70	209011 04/28/97	pBluescript	204	1057	229	365	365	442	1	23	24	22
195	HLMIW92	209011 04/28/97	Lambda ZAP II	205	721	1	244	244	443	1	25	26	46
196	HLTCY93	209011 04/28/97	Uni-ZAP XR	206	2465	988	387	387	444	1	27	28	214
197	HLTDB65	209011 04/28/97	Uni-ZAP XR	207	1480	1	1480	371	445	1	15	16	143
198	HMSHM43	209011 04/28/97	Uni-ZAP XR	208	872	1	872	35	446	1	18	19	36
199	HMSHQ24	209011 04/28/97	Uni-ZAP XR	209	1779	16	148	148	447	1	24	25	36
200	HNFAH08	209011 04/28/97	Uni-ZAP XR	210	2110	592	611	611	448	1	18	19	191
201	HNGAO10	209011 04/28/97	Uni-ZAP XR	211	938	1	107	107	449	1	27	28	30
202	HNGBE45	209011 04/28/97	Uni-ZAP XR	212	1551	1	114	114	450	1	21	22	100
203	HNHAZ16	209011 04/28/97	Uni-ZAP XR	213	997	1	202	202	451	1	24	25	36
204	HNHCM59	209011 04/28/97	Uni-ZAP XR	214	1496	1	1132	165	452	1	28	29	41

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
205	HOSFM22	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	215	1308	501	1308	1081	1081	453	1	46	47	48
206	HPHAC88	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	216	1705	384	1705	549	549	454	1	23	24	24
207	HCDEO95	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	217	999	608	999	273	273	455	1	22	23	54

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently

accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also
5 hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1.

10 Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the
15 actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the
20 generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods.
25 The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

30 The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed

herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or a deposited clone, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the secreted protein.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or a cDNA contained in ATCC deposit Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide encoded by the cDNA contained in ATCC deposit Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide sequence encoded by the cDNA contained in ATCC deposit Z are also encompassed by the invention.

10 Signal Sequences

The present invention also encompasses mature forms of the polypeptide having the polypeptide sequence of SEQ ID NO:Y and/or the polypeptide sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of

predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

5 In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis
10 of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence
15 shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present
20 invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of
25 directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as described below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present
30 invention.

Polynucleotide and Polypeptide Variants

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X, the complementary strand thereto, and/or the cDNA sequence contained in a deposited clone.

5 The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y and/or encoded by a deposited clone.

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many
10 regions, identical to the polynucleotide or polypeptide of the present invention.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the
15 nucleotide coding sequence contained in a deposited cDNA clone or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited clone, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein).
20 Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%,
25 95%, 96%, 97%, 98%, 99% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, the polypeptide sequence encoded by the cDNA contained in a deposited clone, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein).

By a nucleic acid having a nucleotide sequence at least, for example, 95%
30 "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each

100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then

subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference

sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, an amino acid sequences shown in Table 1 (SEQ ID NO:Y) or to the amino acid sequence encoded by cDNA contained in a deposited clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal

residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are

included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be
5 deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma
10 exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and
15 coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule
20 could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or
25 C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular
30 polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification or (v) fusion of the polypeptide with another compound, such as albumin (including, but not limited to, recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or

fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

5 **Polynucleotide and Polypeptide Fragments**

The present invention is also directed to polynucleotide fragments of the polynucleotides of the invention.

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence which: is a portion of that contained in
10 a deposited clone, or encoding the polypeptide encoded by the cDNA in a deposited clone; is a portion of that shown in SEQ ID NO:X or the complementary strand thereto, or is a portion of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:Y. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt,
15 and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in a deposited clone or the nucleotide sequence shown in SEQ ID NO:X. In this context "about" includes the particularly recited value, a value larger
20 or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the
25 invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500,
30 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this

context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed

5 herein. Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y or encoded by the
10 cDNA contained in a deposited clone. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40,
15 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, and ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.
20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-
25 60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also
30 preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and

alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

- 5 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotides encoding these domains are also contemplated.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily
10 identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Preferably, the polynucleotide fragments of the invention encode a
15 polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) polypeptide of invention protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a
20 polypeptide of the invention for binding) to an antibody to the polypeptide of the invention], immunogenicity (ability to generate antibody which binds to a polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

The functional activity of polypeptides of the invention, and fragments,
25 variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the invention for binding to an antibody of the polypeptide of the invention, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using
30 techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using

colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand for a polypeptide of the invention identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, Microbiol. Rev. 59:94-123. In another embodiment, physiological correlates of binding of a polypeptide of the invention to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the invention and fragments, variants derivatives and analogs thereof to elicit related biological activity related to that of the polypeptide of the invention (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Epitopes and Antibodies

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. Z or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:X or contained in ATCC deposit No. Z under stringent hybridization conditions or lower stringency hybridization conditions as defined supra. The present invention further encompasses

polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize
5 to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention
10 encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA
15 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not
20 necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

In the present invention, antigenic epitopes preferably contain a sequence of at
25 least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100
30 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies,

that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985)). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an

immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may
5 be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or
10 antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example,
15 polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)).
20 In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the
25 present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be
30 fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni²⁺ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opinion Biotechnol.* 8:724-33

(1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin

molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be

excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the

epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes
5 antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand
10 binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described
15 supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent
20 ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but
25 do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists
30 for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No.

- 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).
- 10 Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g.,
- 15 Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus

20 or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438;

25 WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include

30 antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of

numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

5 The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal
10 antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and
15 potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be
20 produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not
25 limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma
30 technology are routine and well known in the art and are discussed in detail in the Examples (e.g., Example 16). In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an

immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are
5 selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating
10 monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody
15 able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments).
20 F(ab')₂ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which
25 carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid
30 surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage

gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol.*

Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entirety.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into

mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention.

Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using

techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library

generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe
5 specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the
10 antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor,
15 NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light
20 chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted
25 within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of
30 the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino

acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other
5 alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes
10 from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized
15 antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain
20 antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

25 *Methods of Producing Antibodies*

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment,
30 derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a

polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as

bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems

5 infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO,

10 BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole

15 recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2

20 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which

25 direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic*

30 *Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such

fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein.

Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp^rt- or ap^rt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt,

which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 *Clinical Pharmacy* 12:488-505; Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 5 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, 1993, *TIB TECH* 11(5):155-215); and hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. 10 (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

15 The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in 20 culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second 25 vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic 30 free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad. Sci. USA* 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for
5 the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

10 The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through
15 linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention
20 to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS
25 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may
30 be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any

combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341(1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to

identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred
5 embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags
10 useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used
15 diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent
20 materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No.
25 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone,
30 fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin,

and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{111}In or ^{99}Tc .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- α , TNF- β , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"),

granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports
5 include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For
10 Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results,
15 And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

20 Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can
25 be used as a therapeutic.

Immunophenotyping

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present
30 invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific

epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel *et al*, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A

and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes

the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., ^3H or ^{125}I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., ^3H or ^{125}I) in the presence of increasing amounts of an unlabeled second antibody.

Therapeutic Uses

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any

one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or
5 conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the
10 antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

15 The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

20 The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment,
25 human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and
30 therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention,

including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other

desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific
5 embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or
10 indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be
15 accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun;
20 Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target
25 cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT
30 Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination

(Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can
5 be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can
10 be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human*
15 *Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild
20 disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994)
25 demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In
30 a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in
5 tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

10 In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene
15 transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary
20 developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various
25 methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy
30 encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages,

neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

5 In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or
10 progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

15 In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

20 *Demonstration of Therapeutic or Prophylactic Activity*

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition
25 include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a
30 specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment;

this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when
5 administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)
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In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose
20 (see, e.g., Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by
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use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g.,
5 Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a
10 pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic
15 is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid
20 carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering
25 agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium
30 saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of

the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with
5 routine procedures as a pharmaceutical composition adapted for intravenous
administration to human beings. Typically, compositions for intravenous
administration are solutions in sterile isotonic aqueous buffer. Where necessary, the
composition may also include a solubilizing agent and a local anesthetic such as
lignocaine to ease pain at the site of the injection. Generally, the ingredients are
10 supplied either separately or mixed together in unit dosage form, for example, as a dry
lyophilized powder or water free concentrate in a hermetically sealed container such
as an ampoule or sachette indicating the quantity of active agent. Where the
composition is to be administered by infusion, it can be dispensed with an infusion
bottle containing sterile pharmaceutical grade water or saline. Where the composition
15 is administered by injection, an ampoule of sterile water for injection or saline can be
provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms.
Pharmaceutically acceptable salts include those formed with anions such as those
derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those
20 formed with cations such as those derived from sodium, potassium, ammonium,
calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol,
histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the
treatment, inhibition and prevention of a disease or disorder associated with aberrant
25 expression and/or activity of a polypeptide of the invention can be determined by
standard clinical techniques. In addition, in vitro assays may optionally be employed
to help identify optimal dosage ranges. The precise dose to be employed in the
formulation will also depend on the route of administration, and the seriousness of the
disease or disorder, and should be decided according to the judgment of the
30 practitioner and each patient's circumstances. Effective doses may be extrapolated
from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human
5 antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by
10 modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture,
15 use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically
20 bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body
25 fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder,
30 comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level,

whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods

including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce
5 diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of
10 Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the
15 labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by
20 repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label
25 used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

30 In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with

a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is
5 detected in a patient using magnetic resonance imaging (MRI).

Kits

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified
10 antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present
15 invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

20 In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically
25 immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide
30 antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may

also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in
5 screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be
10 a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present
15 invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the
20 reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip
25 sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated
30 antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound

recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Fusion Proteins

5 Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target
10 cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur
15 through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell
20 or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and
25 specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins
30 consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).)

Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).) Polynucleotides comprising or alternatively consisting of
5 nucleic acids which encode these fusion proteins are also encompassed by the invention.

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a
10 fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for
15 example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker
20 sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for
25 instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides
30 or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral
5 vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate,
10 such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac
15 promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a
20 translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin
25 resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as
30 CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated

or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency
5 from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express the
10 polypeptide of the present invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O₂. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate
15 high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O₂. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia*
20 *pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in
25 the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows
30 expression and secretion of a protein of the invention by virtue of the strong *AOX1*

promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, 5 pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding 10 sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs 15 discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and 20 which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination, resulting in the formation of a new transcription unit (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; U.S. Patent No. 25 5,733,761, issued March 31, 1998; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

30 In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and

Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide sequence of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, Ca -methyl amino acids, Na -methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention encompasses polypeptides which are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, *e.g.*, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as

increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent NO: 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG

to G-CSF), see also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated
5 polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for
10 therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid,
15 glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

20 One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be
25 performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be
30 accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions,

substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The polypeptides of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, *Therapeutics*) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone (including fragments, variants, splice variants, and fusion proteins, corresponding to these polypeptides as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (*e.g.*, containing polypeptides having identical or different amino acid sequences) or a homotrimer (*e.g.*, containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (*i.e.*, polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional
5 embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as,
10 for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion
15 protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (*e.g.*, that recited in the sequence listing, or contained in the polypeptide encoded by a deposited clone). In one
20 instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (*i.e.*, naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the
25 heterologous polypeptide sequence in a fusion protein of the invention.

In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, *e.g.*, US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in an Fc fusion protein of the invention (as
30 described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for

example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous

polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers
5 of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues
10 located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers
15 containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its
20 entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent
25 Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse
30 orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described

herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by
5 reference in its entirety).

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes
10 known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present
15 invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of
20 somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per
25 day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries and computer mapping techniques (See, e.g., Shuler, Trends
30 Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety)..

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see
5 Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

10 The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g., Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-
15 492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage
20 analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated
25 with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural
30 alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide

and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected
5 individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis
10 of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder.

In still another embodiment, the invention includes a kit for analyzing samples
15 for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the present invention and a suitable container. In a specific
20 embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the present invention, where each probe has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder, has already been made according to
25 conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the present invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of polynucleotide of the present
30 invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the present invention or the level of the mRNA encoding the polypeptide in a first biological sample either directly (e.g., by determining or

estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard
5 being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

10 By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains the polypeptide of the present invention or mRNA. As indicated, biological samples include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and other tissue
15 sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic
20 method and/or kits in which polynucleotides and/or polypeptides are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the present invention attached may be used to identify polymorphisms between the polynucleotide sequences, with
25 polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, including cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

30 The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the

preferred form if the polynucleotides are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, *Science* 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, *Nature* 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ($T_{sub.m}$) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention is useful for detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative diseases, disorders, and/or conditions are often associated with inappropriate activation of proto-oncogenes. (Gelman, E. P. et al.,

"The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by
5 insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in
10 some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International
15 Publication Number WO 91/15580) However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580;
20 Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness would not be limited to treatment of proliferative diseases, disorders, and/or conditions of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit
25 proliferative phenotypes.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca
30 Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the

polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456
5 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into
10 polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat or prevent disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective
15 gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute
20 biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of
25 "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative
30 to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a

unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression
5 in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known
10 in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium ($^{99\text{m}}\text{Tc}$), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins
15 can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as
20 deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$), a radio-opaque substance, or a material detectable by nuclear
25 magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5
30 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics

of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which
5 involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high
10 amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the
15 development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat, prevent, and/or diagnose disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different
20 polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a
25 desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat, prevent, and/or diagnose disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce
30 overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover,
5 the polypeptides of the present invention can be used to test the following biological activities.

Gene Therapy Methods

10 Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the
15 invention that operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a
20 polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the invention *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, see Belldegrun et al., J. Natl. Cancer Inst., 85:207-216 (1993); Ferrantini et al., Cancer Research, 53:107-1112 (1993); Ferrantini et al., J.
25 Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura et al., Cancer Research 50: 5102-5106 (1990); Santodonato, et al., Human Gene Therapy 7:1-10 (1996); Santodonato, et al., Gene Therapy 4:1246-1255 (1997); and Zhang, et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are
30 arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs of the invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of polynucleotide sequence of the invention. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotides of the invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or

bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs of the invention are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA , 86:6077-6081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem., 265:10189-10192 (1990), which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication NO: WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of

DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., Felgner et al., Proc. Natl. Acad. Sci. USA, 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

5 Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE),
10 among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine
15 (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2
20 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available
25 to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology, 101:512-527 (1983),
30 which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated.

SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+} -EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta, 394:483 (1975); Wilson et al., Cell, 17:77 (1979)); ether injection (Deamer et al., Biochim. Biophys. Acta, 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun., 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA, 76:3348 (1979)); detergent dialysis (Enoch et al., Proc. Natl. Acad. Sci. USA, 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem., 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA, 75:145 (1978); Schaefer-Ridder et al., Science, 215:166 (1982)), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent NO: 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding polypeptides of the invention. Retroviruses from which the retroviral plasmid vectors

may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

5 The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy, 1:5-14 (1990), which is incorporated herein by
10 reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO₄ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

15 The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding polypeptides of the invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express polypeptides of the invention.

 In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with
20 polynucleotides of the invention contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses polypeptides of the invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional
25 mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al., Am. Rev. Respir. Dis., 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science, 252:431-434 (1991);
30 Rosenfeld et al., Cell, 68:143-155 (1992)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al. Proc. Natl. Acad. Sci. USA, 76:6606 (1979)).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.*, 3:499-503 (1993); Rosenfeld et al., *Cell*, 68:143-155 (1992); Engelhardt et al., *Human Genet. Ther.*, 4:759-769 (1993); Yang et al., *Nature Genet.*, 7:362-369 (1994); Wilson et al.,
5 *Nature*, 365:691-692 (1993); and U.S. Patent NO: 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express E1a and E1b, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other
10 varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of
15 infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*,
20 using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, *Curr. Topics in Microbiol. Immunol.*, 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is
25 limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell
30 integration. The polynucleotide construct containing polynucleotides of the invention is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor

Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses.

- 5 Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct of the invention. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express the desired gene product.

- 10 Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding the polypeptide sequence of interest) via homologous recombination (see, e.g., U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO
15 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA, 86:8932-8935 (1989); and Zijlstra et al., Nature, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

- Polynucleotide constructs are made, using standard techniques known in the
20 art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous
25 polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

- The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same
30 restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the

amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

The polynucleotides encoding polypeptides of the present invention may be administered along with other polynucleotides encoding other angiogenic proteins. Angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

Preferably, the polynucleotide encoding a polypeptide of the invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle

accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium

5 phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers. (Kaneda et al., Science, 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is
10 administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a
15 patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery
20 vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be
25 performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA, 189:11277-11281 (1992), which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the
30 gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a

polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian. Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly

15 Biological Activities

The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

Polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

25

Immune Activity

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis,

30

producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or
5 infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to
10 treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the
15 present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked
20 immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type),
25 Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID),
30 common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

5 Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare
10 lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

15 In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or
20 antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic
25 alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented,
30 diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary

inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention

In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or

agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain

injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are
5 characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

Because inflammation is a fundamental defense mechanism, inflammatory
10 disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis,
15 chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis,
20 peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose,
25 prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues.

Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or
30 antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides,

antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

5 In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

10 Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an
15 existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

20 In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art.

30 In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In

another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, 5 cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal 10 immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group 15 consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseries meningitidis*, 20 *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may 25 be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an 30 immune response to Plasmodium (malaria) or Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat

infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

10 In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an
15 immune response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of
25 immunosuppressive therapies.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

30 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants
10 (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment,
15 compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost
20 immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists
30 or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious

mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one
5 embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to
10 modulate the immune system.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more
20 rapidly their susceptibility profile would likely change.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the
30 pretreatment of bone marrow samples prior to transplant.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based

therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of
5 activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

10 In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of
15 blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

30 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal

gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance
5 to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

10 The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit
15 complement mediated cell lysis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult
25 respiratory distress syndrome (ARDS).

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of
30 the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized

by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne
5 infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media,
10 conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal
15 dysfunction anemia, thrombocytopenia, and hemoglobinuria.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a
20 subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be
25 prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed
30 diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals,
10 such as, for example, an individual who has undergone a partial or complete splenectomy.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the
15 invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

20 In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of
25 producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of
30 monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention in an organ system listed above.

Blood-Related Disorders

- The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing
- 5 hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes.
- 10 Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.
- 15 In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the
- 20 polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with
- 25 mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass
- 30 machines).

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to

prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

5 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes,
10 lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the
15 present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for
20 example eosinophilia.

 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

 Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may
25 be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or
30 antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious

anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may
5 be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias
10 arising from drug treatments such as anemias associated with methyl dopa, dapsone, and/or sulfadiazine. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis,
15 glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the
20 polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or
25 agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak
30 syndromes, thromboxane A2 dysfunction, thrombasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophiliac syndromes such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary

Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored
5 using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in
10 a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug
15 treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or
20 associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis
25 may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer.

Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in
30 diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or

antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in
5 specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the
10 present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment,
15 anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

20 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies,
25 and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

30 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or

macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myeloid metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

5 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

10 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

15 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

20

Hyperproliferative Disorders

In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

30 For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune

response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

5 Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital
10 tract.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute
15 Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related
20 Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer,
25 Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic
30 Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue

Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related
5 Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular
10 Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant
15 Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and
20 Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer,
25 Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma,
30 Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive

Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal
5 Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or
10 treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal
15 growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated
20 with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic
25 hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia,
30 senile sebaceous hyperplasia, and verrucous hyperplasia.

Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders

which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, 5 epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

Dysplasia is frequently a forerunner of cancer, and is found mainly in the 10 epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, 15 and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atridigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital 20 ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, 25 familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial 30 dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia,

pseudoachondroplastic spondyloepiphyseal dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphyseal dysplasia, and ventriculoradial dysplasia.

Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including
5 polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

In another embodiment, a polypeptide of the invention, or polynucleotides,
10 antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or
15 agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein,
20 may be used to treat acute myelogenous leukemia.

Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the
25 inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer,
30 intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and

ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes
5 viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

10 Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute
15 myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including,
20 but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer,
25 squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor,
30 lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma,

pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells.

In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By

"biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in
5 tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described
10 disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may
15 be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of
20 the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering
25 a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or
30 activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present

invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins

(See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

5 Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4
10 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions
15 containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic
20 and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and
25 immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Renal Disorders

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the
30 present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented,

and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

- 5 Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome,
- 10 membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal
- 15 glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting from urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis,
- 20 nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

- In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria,
- 25 nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus,
- 30 analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE),

Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g.,

5 glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema,

10 hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous

15 injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more

20 detail below. Methods of delivering polynucleotides are described in more detail herein.

Cardiovascular Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present

25 invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral

30 arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia,

patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects,

- 5 Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac
 10 edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease,
 15 ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine
 20 Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia,
 25 Torsades de Pointes, and ventricular tachycardia.

Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia,
 30 tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular

stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include, but are not limited to, coronary disease, such as
5 angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema,
10 aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's
15 disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include, but are not limited to, dissecting aneurysms, false
20 aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery
25 occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis,
30 Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia

(including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include, but are not limited to,

5 coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but

10 is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or

20 topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

25 Respiratory Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

Diseases and disorders of the respiratory system include, but are not limited

30 to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's

- nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomonas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).
- Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis, fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia spp.*), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis,

desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial),
5 bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

10 The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive
15 processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization
20 including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J.*
25 *Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

30 The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present

invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*,
5 Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists
10 may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder,
15 thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and
20 Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a
25 catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These
30 disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy,

retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

10 For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

15 Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

25 Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion,

but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly
5 after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-
10 3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or
15 agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the
20 compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

25 Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

30 Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or

agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the polynucleotides, polypeptides, agonists and/or agonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochelominalia quintosa), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a

peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch
5 granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal
10 surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic
15 compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-
20 angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the
25 site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly
30 preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may
5 be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive
10 Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium,
15 molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes
20 include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include
25 oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl
30 complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum

(VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

- 5 A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence
10 of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem.
15 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987);
20 Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

25 Diseases at the Cellular Level

- Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include
30 cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma,

lymphoma, endothelioma, osteblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related
5 glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, polynucleotides, polypeptides, and/or antagonists
10 of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or
15 metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and
20 non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic
25 cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor,
30 cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma,

craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as
5 agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's
10 disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and
15 liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is
20 provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present
25 invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing
30 conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or

antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepidermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentoplastic graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis.

- 5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat
- 10 gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly.
- Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or
- 15 antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect
- 20 the intestinal mucosa from injurious substances that are ingested or following surgery.
- Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

- Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to
- 25 various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke
- 30 inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as

agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins
10 known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists
15 of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

20 Neural Activity and Neurological Diseases

The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides,
25 and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the
30 following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or

ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated

with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev.*

Neurosci., 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or
5 Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral
10 ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or
15 antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or
20 detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency,
25 pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as
30 ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell

leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

5 include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's

10 Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

15 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as

20 multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis,

25 encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-

30 Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

- 10 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as
- 15 Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as
- 20 Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

- Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include
- 25 cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell
- 30 leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis,

transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms
5 such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis
10 such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity,
15 encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie
20 Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing
25 disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders
30 such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman

syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as

5 diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision

10 defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron

15 disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia,

20 amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barré-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-

25 Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic

30 Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases

such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention
5 include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as
10 polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

15

Endocrine Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine
20 system.

Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine
25 system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

30 Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with

pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include

5 disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the

10 pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous

15 thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the

20 hypothalamus.

In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat,

25 prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin

30 dependent diabetes mellitus, IDDM).

In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to

diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or
5 antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, and/or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and
10 other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the
15 "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's
20 weight. In specific embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene
25 and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including
30 cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells,

cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example,

5 polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders

10 associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

Reproductive System Disorders

15 The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and
20 diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and
25 orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm
30 production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate
5 neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica
10 obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis,
15 giant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and
20 impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or
25 disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and
30 gynecomastia.

Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of

diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenositis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

- 10 Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

- 25 Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

- 30 Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example,

cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as
5 early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio
10 placenta, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral
15 valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematositis, rheumatoid arthritis, myasthenia
20 gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal),
25 breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis,
30 mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and

agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

5

Infectious Disease

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and
10 differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

15 Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae,
20 Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae,
25 Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue
30 syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic

fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific

5 embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment

10 polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-

15 Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthraxis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium difficile*,

20 *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diphtheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia,

25 Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae* and *Mycobacterium tuberculosis*), Vibrio (e.g., *Vibrio cholerae*), Neisseriaceae (e.g., *Neisseria gonorrhea*, *Neisseria meningitidis*), Pasteurellaceae, Proteus, Pseudomonas

30 (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningioccus, Pneumococcus and Streptococcus (e.g., *Streptococcus*

pneumoniae and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., meningitis types A and B), chlamydia, syphilis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, nosocomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Schistosoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be

used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of

non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Gastrointestinal Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma)), and ulcers, such as peptic ulcers.

Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile

hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, 5 hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma)], peliosis hepatis, erythrohepatic porphyria, hepatic 10 porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and 15 glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, 20 acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous 25 adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases 30 (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis,

amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal
5 volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal
10 lymphangiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia,
15 gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and
20 hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus,
25 esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's
30 diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome),

stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)),
5 hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Chemotaxis

10 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then
15 fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the
20 number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as
25 agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

30 A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The

binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

5 Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural
10 receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

 Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane
15 containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

 The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving
20 competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

 Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate
25 compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

 Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The
30 antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed
5 wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are
10 exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-
15 transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and
20 exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

25 Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R.

Biotechniques 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and $^3\text{[H]}$ thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the

uptake of $^3\text{[H]}$ thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of $^3\text{[H]}$ thymidine. Both agonist and antagonist compounds may be identified by this procedure.

5 In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following
10 interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

15 All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from
20 suitably manipulated cells or tissues.

 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of
25 identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

5 As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention
10 (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate
15 episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

20 By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes
25 known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a
30 non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of

benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

5 **Drug Screening**

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected
10 compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in
15 such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation
20 of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the
25 present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a
30 particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present

invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

10 This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Polypeptides of the Invention Binding Peptides and Other Molecules

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the polypeptide of the invention binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

25 This method comprises the steps of: contacting a polypeptide of the invention with a plurality of molecules; and identifying a molecule that binds the polypeptide of the invention.

The step of contacting the polypeptide of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptide of the invention on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptide of the invention. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptide of the

invention. The molecules having a selective affinity for the polypeptide of the invention can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptide of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptide of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptide of the invention and the individual clone. Prior to contacting the polypeptide of the invention with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for a polypeptide of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptide of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptide of the invention, or alternatively, unbound polypeptides, from a mixture of the polypeptide of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction.

Such a wash step may be particularly desirable when the polypeptide of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide
5 libraries which can be screened for molecules that specifically bind to a polypeptide of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature*
10 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al.,
15 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, *Science* 249:386-390; Devlin et al., 1990, *Science*, 249:404-406; Christian, R. B., et al., 1992, *J. Mol. Biol.* 227:711-718; Lenstra, 1992, *J. Immunol. Meth.* 152:149-157;
20 Kay et al., 1993, *Gene* 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:9022-9026.

25 By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically
30 transformed combinatorial library, is described by Ostresh et al. (1994, *Proc. Natl. Acad. Sci. USA* 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is

great. For example, Ecker and Crooke, 1995, *Bio/Technology* 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a polypeptide of the invention can be carried out by contacting the library members with a polypeptide of the invention immobilized on a solid phase and harvesting those

library members that bind to the polypeptide of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

5 In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to a polypeptide of the invention.

Where the polypeptide of the invention binding molecule is a polypeptide, the
10 polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

15 Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine.

20 Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a polypeptide of the invention binding
25 molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a polypeptide of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

30 The selected polypeptide of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited
5 clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA
10 or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research, 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251:1300
15 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These
20 experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is
25 heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA
30 oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense

RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or
5 a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard
10 in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early
15 promoter region (Bernoist and Chambon, *Nature*, 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell*, 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster et al., *Nature*, 296:39-42 (1982)), etc.

20 The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA,
25 forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the
30 invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, *e.g.*, the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at
5 inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5' - or 3' - non- translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should
10 include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50
15 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or
20 phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556 (1989); Lemaitre et al., *Proc. Natl. Acad. Sci.*, 84:648-652 (1987); PCT Publication
25 NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, *e.g.*, PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, *e.g.*, Krol et al., *BioTechniques*, 6:958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, *Pharm. Res.*, 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide,
30 hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are

commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990)). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5' -UG-3' . The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of

the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention

Other Activities

The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide

may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells
5 of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's
10 disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

The polypeptide of the present invention may be also be employed to prevent
15 skin aging due to sunburn by stimulating keratinocyte growth.

The polypeptide of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone
20 marrow cells when used in combination with other cytokines.

The polypeptide of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues.

The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

25 The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as
30 body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to

modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive diseases, disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the
5 nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

10 Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ
15 ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule
20 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization
25 conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type
30 Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the
5 ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
10 sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human
15 cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological
20 sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained
25 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences
30 comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence

selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least

95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise
5 a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence
10 encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the
15 amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the
20 Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid
25 sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

30 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human

cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a

sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained
5 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

10 Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at
15 least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

20 Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules
25 in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in
30 Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone
5 identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of
10 making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making
15 an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and
20 said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

25 Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

30 The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-

human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

- 5 In specific embodiments of the invention, for each "Contig ID" listed in the fourth column of Table 2, preferably excluded are one or more polynucleotides comprising, or alternatively consisting of, a nucleotide sequence referenced in the fifth column of Table 2 and described by the general formula of a-b, whereas a and b are uniquely determined for the corresponding SEQ ID NO:X referred to in column 3
- 10 of Table 2. Further specific embodiments are directed to polynucleotide sequences excluding one, two, three, four, or more of the specific polynucleotide sequences referred to in the fifth column of Table 2. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby
- 15 incorporated by reference in their entirety.

TABLE 2

Gene No.	cDNA Clone ID	NT SEQ ID NO: X	Contig ID	Public Accession Numbers
1	HLHDS67	11	396448	T84556, R77553, H77877, H96723, N22894, N24112, N25474, N31281, N31410, N31809, N42470, N58904, N59834, N67726, W03552, W15430, W78090, W79576, W94783, W95299, AA112608, AA126875, AA127799, AA133859, AA169532, AA169601
2	HLHDZ58	12	396869	R44557, R44557, H15251, H16568
10	HOUBE18	20	407070	T97913, R21634, R47833, R49975, R54690, R55015, R55153, R62188, R64576, R80153, R80154, R81484, R81724, H13709, H13762, H49782, N33449, N34466, N42422, N42873, N50673, N53663, N73029, W44598, W73379, W73403, AA088385
11	HOUDL69	21	396821	T98572, T98573, T99692, R46104, R46177, R46104, R46177, R77699, R77698, R81185, R81291, R84758, R84835, N73056, W88438, W89202
12	HPMFI71	22	407378	R53416, R54007, H14084, H45951, H75270, H75382, N27106, N40516, W37083, W37084, W72173
15	HPTBB03	25	399928	T58022, T86930, R11711, T83207, T86107,

				T96449, R17686, R36056, R36058, R49138, R49140, R53540, R53651, R49138, R73230, R76352, H06054, H13390, H14662, H17478, H17586, H24833, H29049, H29151, H92319, H92379, N24774, N32793, N42234, N94618, W15347, W31392, W31984, W39439, W95395, W95353, AA088664, AA088803, AA102451, AA130481, AA130482, AA143411, AA143667, AA146597, AA148224, AA148225, AA156280, AA156391, AA158602, AA158959, AA158958, AA158971, AA158970, AA164777
16	HPTWA66	26	614220	R32953, R48005, R52174, R53999, R94185, N58829, N75247, W86429, AA024852, AA024935, AA101581, AA101582, AA121348, AA121367, AA135194, AA135274, AA149607, AA149718, AA181794, AA461476, AA460122
16	HPTWA66	219	408041	T56759, T63654, R48005, R53999, N58829, W86429, AA024852, AA101582, AA121348, AA135194, AA149607
17	HPTWC08	27	396380	T77302, R21500, R35136, R41732, R42882, R49522, R41732, R42882, R49522, H20938, H41732, R85141, R88669, R88670, R88816, R89638, R89643, R90743, R90777, R90782, AA040665, AA127052
18	HRGCZ46	28	400796	T48000, T49441, T62059, T65112, T65179, T92082, T78688, T79315, T83158, T85864, R15724, R17015, R18665, R22674, R45966, R45966, H24497, H27416, H44475, N50917, N94040, W17223, W40134, W92875, W94259, W94444, W94673, W94957, W95142, W95598, W95853, N89726, AA045010, AA081572
19	HSAVU34	29	724060	T52500, T67115, T67116, T90451, R10617, R10618, T82973, H05156, H10930, H10931, H56169, H56385, H66700, H66701, H73933, H74126, N32119, N57071, N59463, N67109, N71110, N74124, N74136, W02046, W05471, W19600, W23443, W24737, W35258, W37178, W57794, W58026, W81529, W81530, AA079135, AA121270, AA121423, AA151481, AA151504, AA220993, AA226857, AA250826, AA252645, AA428383
19	HSAVU34	220	396807	T52500, T67115, T67116, T90451, R10617, R10618, T82973, H05156, H10930, H10931, H56169, H56385, H66700, H66701, H73933, H74126, N32119, N57071, N59463, N67109, N71110, N74124, N74136, W02046, W05471, W19600, W23443, W24737, W35258, W37178, W57794, W58026, W81529, W81530, AA079135, AA121270, AA121423, AA151481, AA151504
20	HSDFW61	30	407496	T55525, R10577, R10576, R11610, T78468, T78545, T95431, R01101, R19400, H55969, H84552, N24342, N26542, N35654, N39425, N48541, N64022, N73360, N78008, N95084, W23486, W67558, W67606, W69403, W73515, W73497, W74493, W79090, N89865, AA015719, AA034158, AA053058, AA053402, AA127181

22	HSOAJ55	32	829668	T90006, R09378, R09379, R12195, T82827, T84829, R23136, R23137, R23150, R23149, R23901, R23902, R35690, R39919, R49327, R49327, H08646, H08645, H52709, H52986, H67120, H81426, H97481, N20907, N31009, N51872, N51878, N54463, N76574, W37292, W37826, AA052963, AA053019, AA053505, AA129021, AA129020, AA133655, AA133656, AA130953, AA573417, AA746147, AA879142, AA938486, D82776, D82683, W23236, C17493
22	HSOAJ55	221	361281	T90006, R09378, R09379, R12195, T82827, T84829, R23136, R23137, R23150, R23149, R23901, R23902, R35690, R39919, R49327, R49327, H08646, H08645, H52709, H52986, H67120, H81426, H97481, N20907, N31009, N51872, N51878, N54463, N76574, W37292, W37826, AA052963, AA053019, AA053505, AA129021, AA129020, AA133655, AA133656
24	HSXAM05	34	396445	H41055, H86278, H86277, N36167, N49355, N99253, W30680, AA187548
25	HSXAS67	35	396441	R43052, R46024, R54365, R46024, R59349, H29581, AA018134, AA128286, AA165397
26	HTDAF28	36	396835	R32754, R65808
30	HTPBW79	40	581435	T58875, T69236, R12437, R13448, R37325, R37361, N52277, W38735, W72124, AA009696, AA088448, AA181149, AA181148
30	HTSEV09	223	396459	T54203, T58875, T69236, R37325, R37361, R72050, N52277, N59026, N72929, W38735, W72124, W77848, AA009696, AA009415, AA088448, AA088502, AA181149
31	HJPCD40	41	401227	R01078, H47562, H58468, N31052, N92318, N93676, N93667, W24390, W79518, W79405, W86336, W95427, W95554, AA002106, AA005054, AA009752, AA009751, AA022648, AA022637, AA035194, AA143435, AA157417
33	HTWCI46	43	407490	T71107, R07491, R07544, R02367, R02473, R12602, R74032, R74123, R79290, R81173, R81277, R86952, H49320, N54909, AA196897
34	HTXGI75	44	396652	H11517, H61199, H96603, N24777, N28311, N28909, N73009, N73300, W02991, W16442, W23776, W35231, W39312, W79539, W79620, AA026925, AA026924, AA079258, AA079257, AA085612, AA112862, AA143350, AA143349, AA147394, AA147466, AA147465, AA156313
35	HWTBF59	45	740670	T47527, T47528, T89276, T84349, R00444, R00445, R50263, R50726, R51643, R62425, R73541, H05078, H38730, H68907, H68809, H75646, H75453, H75452, H81932, H82027, N32427, N36140, N37025, N42766, N44144, N52649, N56850, N68925, W02115, W03625, W15447, W20382, W32576, W35117, W39632, W44562, W47604, W69467, W69551, W73740, W86128, W86148, W95672, AA024821, AA024927, AA025859, AA025860, AA046830, AA046873, AA126258, AA134986, AA135083, AA150759, AA150682, AA235603, AA236621,

				AA236897, AA464236, AA419070, AA419131, AA428777, AA429067, AA428056
35	HWTBF59	224	361287	T47528, T89276, R00445, R50726, R51643, R62425, R73541, H05078, H38730, H68907, H75646, H75453, H81932, N32427, N36140, N37025, N52649, N56850, N68925, W02115, W15447, W20382, W32576, W39632, W44562, W69551, W73740, W86128, W86148, W95672, AA024821, AA024927, AA025859, AA025860, AA046830, AA126258, AA134986, AA135083, AA150759
36	HADAE74	46	409832	T46989, T46988, T65134, T65203, R17426, R23237, R23312, R42660, H60654, H75862, H75861, N24093, N31388, W56001, W56290, AA047063, AA047064, AA046111, AA046198, AA098961, AA098828, AA182785, AA187777, AA191047
38	HATEF60	48	410124	T64995, R17261, R41876, R68452, R68454, H21498, H98622, N25142, N30676, N33908, N67489, N99057, W30718, AA035240, AA035318, AA043654, AA043655, AA046927, AA046984, AA133159, AA133204, AA131580, AA131629, AA132763, AA132857
39	HBMSN25	49	412010	R34536, R49053, R85085, R87831, R87846, AA199833
40	HCDAR68	50	411482	H24669, AA055330, AA055927
41	HCE3J79	51	409610	T66611, T81694, R15985, R44533, R50983, R52279, R52280, R54333, R46724, R44533, R61702, R63949, R64049, R72902, R73540, H42845, H43343, H43397, H44022, H44570, H44569, H59659, H74011, H75604, N53399, W60971, W61218, AA024497, AA024619, AA132738, AA173154, AA188369, AA237026
42	HMDAN54	52	411318	T78112, R19702, R37848, R44258, R44258
43	HCECA49	53	409543	T48789, T48790, T52689, T52690, T54143, T57627, T60334, T63169, T64611, T68165, T73770, R09683, R05784, R05870, R23705, R24243, R25436, R26263, R26661, R31482, R33617, R52663, R55790, R64491, R65588, R66756, R74348, R74447, R77767, R77861, H24648, H24647, H25483, H30170, H42201, H61272, H74187, H73366, H84457, H96852, H97161, N21258, N24067, N25891, N32256, N35943, N39665, N59887, N74237, N75946, N77028, N91815, N94382, W16791, W37991, W42625, W42503, W42504, W45097, W46997, W47010, W47011, W47035, W58226, W60191, W74239, AA011342, AA053421, AA053142, AA069730, AA069687, AA071401, AA079362, AA088476, AA088867, AA099339, AA098900, AA099401, AA099509, AA099626, AA100481, AA111899, AA112344, AA128689, AA130068, AA130069, AA133988, AA134388, AA130699, AA131164, AA135908, AA143614, AA148147, AA151655, AA151855, AA150148, AA152217, AA150454, AA156656, AA156942, AA158064,

				AA158065, AA160927, AA167640, AA173558, AA173723, AA188571, AA188806, AA190996, AA191121
44	HCEEC15	54	409527	R69381, R69382
45	HCESF40	55	616396	R13472
45	HCESF40	225	411082	R13472, R37382, H49570, N55573
46	HCFMV39	56	410579	R91923, R92247
48	HCNAP62	58	411042	H21798, AA149965
49	HCRAF32	59	409522	AA194845
53	HE2AV74	63	411019	R33678, R35656, R37491, R56683, H14646, H61361, H62387, AA131445, AA131558
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56	HE2OF09	66	371407	N68961, W00660, W46419, W48762, W49781
57	HE6EU50	67	411998	R10241, R10723, R10745, W86987, AA069424, AA069425
58	HE9HU17	68	411183	T50250, R08461, R08467, R14041, R17411, R33516, R42644, R42644, H01172, H01257, H12436, H12435, H22405, H22406, H46453,

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61	HELDY74	71	410281	T66450, R15824, R51635, W72803
62	HEMAE80	72	409495	T71556, T90634, T82005, T83161, H57113, H61567, AA233071
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64	HFGAB89	74	408358	T89093, R60840, H16750, H51569, H51939
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91	HPCAL49	101	411321	N66498
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97	HRGBR28	107	410144	T74132, R19091, H16341, H16424, R87393, W74106, AA120808, AA160124
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109	HTSHE40	119	411287	R49564, R49564, H72036, W90622
111	HTWBY29	121	410175	T59381, R19528, R43882, R43882, R55664, R55665, H17451, H17555, R88491, R90802, R90803, AA019030, AA021487, AA080905,

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113	HCE3Q10	123	412333	R12129, R15338, R36062, H08308, H14720, H40798, H38530, R88252, R88963, N45514
114	HCEVR60	124	414534	T94052, R63094, R63141, W72684, W73520, W73503, W77790, AA075563, AA075558
115	HDTAW95	125	412472	R46762, R46857
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134	HBGCB91	237	371337	T69855, R08029, R08078, H08339, H24045, H42902, H42973, H58361, H58750, H80028, H94211, N70685, N99825, W42711, W42904, W57667, W60487, W60773, AA009753, AA135410
135	HBMTD81	145	410544	R21916, R22565, R99043, AA046203, AA046283, AA055141, AA173411, AA173467
136	HBXGK12	146	415649	T55067, R05951, R76538, R76945, R77034, R79544, R79545, H00668, H61203, H62107, N74280, N77879, W04380, W05836, W07303, AA026385, AA026375, AA047358, AA055622, AA112556, AA159861, AA255749
137	HFKFJ07	147	423130	AA152460
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141	HE8EY43	151	407475	R74382, R74394, H24509, H89226, N22621, W37881, W37943, W76005, AA215347
142	HFCEB37	152	411345	H06701
143	HFTCT67	153	412026	H40744, N94366, AA187325, AA188450
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148	HKLAB16	158	419037	R02500, R32757, R37842, R70640, R82407, W32933, W35369, N90561, AA026880,

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154	HOECU83	238	419012	R34106, R34105, AA224458
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163	HBM TY28	173	422688	T54996, T55162, T81957, H40448, H40449, R96511, R96556, H59080, H60352, N58089, N76050, W04455, AA005161, AA004218, AA011395, AA011432, AA116050
164	HBMVP04	174	812281	H82435, H82698, N53899, W04955
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165	HCDD878	175	422696	T80138, R05721, R05722, R40720, R51388, R40720, R60772, H77587, H91710, H91811, N52332, N62896, N75102, W01336, W24829,

				W56236, W78702, W80502, AA031936, AA031937, AA034077, AA046609, AA046724, AA129906, AA129905, AA133809, AA150149, AA152218, AA235941, AA236885
167	HCEZS40	177	422714	R12037, R18992, R44878, R44878, H56172, H56388, H58079, H79475, H97586, N20466, N25493, N28755, N50120, N62820, W01355, W74545, W74486, W93543, AA128184, AA126379
168	HCFNF11	178	422712	H80152, AA010492, AA167414, AA167418, AA167415, AA167426, AA167425, AA167419, AA171736, AA172019
169	HCRBL20	179	744946	T89241, H88386, H88454, H88386, N46536, N63060, W93935, W93936, AA075562, AA075557, AA180173, AA180147, AA194932, AA194931, AA194884, AA195588, AA213530, AA243504, AA243357, AA422037
169	HCRBL20	242	422383	T89241, H88386, H88454, H88386, N46536, N63060, W93935, W93936, AA075562, AA075557, AA180147, AA194932, AA194931, AA194884, AA195588, AA213530, AA243504, AA243357
171	HDSAP81	181	422719	N39609, AA011604
172	HE2CT29	182	420020	N74326
173	HE8MG65	243	422740	T56650, T57256, T63714, T73914, T73938, T73946, T73970, T77203, R22170, R22171, R24271, R24380, R27064, R27990, R28253, R28546, R33988, R39548, R60886, R66279, R66278, R67307, R71201, R71202, H02943, H03083, H03084, H04243, H04760, H04851, H06938, H06939, R84922, R91805, R91804, R93954, R93953, R94083, R94129, H52707, H69823, H69832, H84985, H87352, H87893, H94285, N24258, N26510, N31711, N33488, N35085, N35563, N42365, N43879, N53729, N67539, N73915, N77452, N78653, W45116, W78900, W84673, AA015592, AA018305, AA018631, AA018727, AA019837, AA022837, AA022960, AA039983, AA040630, AA156047
174	HE9FB42	184	828253	T71135, T81630, T82274, T83563, R66636, H04574, H18490, N46661, N47628, N52212, N53127, N53634, N62209, N66750, N76507, N79940, W73330, W84546, AA149684, AA164834, AA164833, AA171498, AA171599, AA187239, AA187687, AA187903, AA186756, AA227149, AA227342, AA233128, AA233262, AA233728, AA258430, AA259060, X93861, AA603886, AA568710, AA639952, AA974278, W26196, W84460, C20754, AA090438, AA094076
174	HE9FB42	244	420024	T71135, T81630, T82274, T83563, N46661, W73330, AA149684, AA164833, AA171599, AA187239, AA187903, AA186756, AA227149, AA227342
175	HEMAM41	185	741647	R40658, R40658, N62855
175	HEMAM41	245	419870	R40658, R40658, N62855
176	HEMCV19	186	423219	R39576, R39644, R55519, R55520, H25585,

				H25630, H42497, H43485, R95168, H73675, H73419, H80718, H80719, W95391, W95348, AA034079, AA044081, AA187305, AA187096
178	HETAR54	188	422765	R22877, R78124, H86507, N34893, N95529, W20289, W24342, W32533, W32670, N90669, AA019416, AA019318, AA026402, AA027311, AA037586, AA054647, AA252682
179	HETBX14	189	806447	W60282
179	HETBX14	247	422659	W60282
180	HFGAB48	190	422777	R42520, R42520, N64660, N80095
181	HFKFI40	191	423226	T47877, T47937, T51505, T75501, T89199, T85240, T85406, R20055, R28467, R31273, R31879, R76266, H03224, H04016, H16963, H30109, N53759, N58780, N62962, N77467, N79865, N81078, W07419, W57548, W68669, W68772
182	HFXHN68	192	422549	T87904, T87997, R10903, R10955, H64853, N63499, N74353, N74407, N94712, W02620, W03115
183	HGBFO79	193	422794	T74861, R54514, R76898, R77063, R79667, R79856, R84453, R98071, H54089, W40292, W46517, W88866, AA203205
184	HGLAM56	194	423223	AA256641, AA256642
187	HHPSD37	197	422805	R44397, R44397, N32549, N41894, AA085999
188	HHPSF70	198	422809	R26136, H08855, H41065, H55993, H80007, H83746, H83889, H88534, H88580, H89097, H89200, N22006, N45466, N45508, N51670, N51854, N54118, N62627, N71208, N78398, AA018235, AA019116, AA131865, AA131952, AA148774, AA148523
189	HHSK25	199	422813	T92909, T93001, T95997, R61024, H19116, H24430, H24459, R94331, H67161, H68562, H73892, H73918, H74085, H74110, H78993, H81466, H81767, H81766, H82583, H91720, H91821, H99152, N20388, N22843, N24401, N24496, N25453, N28651, N35075, N36359, N43815, W92746, W92869, AA057815
190	HIASB53	200	422811	T68050, R97204, N42257, AA046836, AA047007, AA157267, AA157180, AA186993, AA188308, AA196715
191	HJABZ65	201	419857	N75833, N78710, N91897, W44720, W44764, N90606, AA135838
192	HJPBB39	202	422649	T66427, R15801, R14623, R33639, R45609, R51011, R51118, R45609, R66101, R67704, H17989, H17990, N94819, W17083, W67749, W68029, W74094, W79385, W94890, W92054, AA007307, AA007469, AA054550, AA054558, AA054610, AA054618, AA054521
193	HLHSK94	203	422828	R55809, H83295, N92239, W37154, W38638, N90902, AA017680, AA040604, AA040705
194	HLHTC70	204	422829	R61522, H08810
196	HLTCY93	206	422848	T50389, T50520, T55419, T55495, T55974, T57220, R34591, R34592, R69726, H21148, R85777, R99233, H61311, H62351, H85185, H88299, N23288, N32662, AA005068, AA007333, AA007334, AA036884, AA044715, AA044907,

				AA045458, AA046500, AA045654, AA115936, AA126775, AA133605, AA133606, AA133980, AA181633, AA182611
197	HLTDB65	207	419864	T88814, T78480, T78565, T84197, T96608, T96718, T96898, T96899, R01674, R02614, R62952, R63004, H01169, H01254, H40397, H53915, H54535, H86324, N23958, N28602, N31859, W17062, W40144, W49624, N89648, AA019070, AA019151, AA134914, AA136931, AA137028, AA148976, AA148977, AA196164, AA196293
199	HMSHQ24	209	422565	R16159, R55052, R59723, R72647, H60244, N33957, N79519, N79654, AA032239, AA033647, AA156948
200	HNFAH08	210	420031	R62825, H69909, H69910, H69910, N25612, N34210, AA056610, AA251839, AA251814
205	HOSFM22	215	412025	T90315, T90402, R23872, R30787, R76172, R77141, R80565, H00726, H01049, H01153, H04603, H04630, H12817, H79113, H82795, H95178, N42743, N68145, N75220, N94419, N98917, W19432, W30766, W31142, W46805, W46923, W48861, W79735, W92123, AA046579, AA046665, AA046966, AA057191, AA127892, AA129011, AA136002, AA136874, AA136903, AA152237, AA152204, AA199930, AA203584
206	HPHAC88	216	411423	R19567, R35876, R35877, R48573, R48673, H41417, R85943
207	HCDEO95	217	371706	H69632, H70475, N66605, AA026327

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

5 Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector.
 10 Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being
 15 isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited</u>
	<u>Plasmid</u>	
	Lambda Zap	pBluescript (pBS)
20	Uni-Zap XR	pBluescript (pBS)
	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
25	pCMVSPORT 3.0	pCMVSPORT 3.0
	pCR [®] 2.1	pCR [®] 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap
 XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos.
 30 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are

commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl ori of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

- 5 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).)
- 10 The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate.
- 15 These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

- Alternatively, two primers of 17-20 nucleotides derived from both ends of the
- 20 SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 μg of the above cDNA template. A convenient reaction mixture is
- 25 1.5-5 mM MgCl_2 , 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and
- 30 the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X.,
5 according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by,
10 among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The
15 purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to
20 manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

25 An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C.
30 Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose

gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

5 A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product
10 into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning
15 sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which
20 expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid
25 culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to
30 increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic

agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with
5 high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is
10 eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear
15 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at
20 4 degree C or frozen at -80 degree C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains:
25 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

30 DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA

insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

- 5 The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

- 10 The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10 degree C.

- 15 Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

- 20 The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

- 25 The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

- 30 Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μ m membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus

Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40")

is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation

mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

- 5 Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a
- 10 microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is
- 15 then incubated for 5 hours at 27 degrees C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

- After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life
- 20 Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a
- 25 micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

- 30 To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of

infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of ^{35}S -methionine and 5 uCi ^{35}S -cysteine (available from Amersham) are added.

- 5 The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the
10 produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and
15 signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early
20 promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109),
25 pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing
30 the polynucleotide integrated into a chromosome. The co-transfection with a

selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing
5 cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279
10 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

15 Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g.,
20 with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate
25 restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide.
30 Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

5 The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

10 Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 a pC4 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are
15 seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in
20 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 µM, 2 µM, 5 µM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 µM. Expression of the desired gene product is analyzed,
25 for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For
30 example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to

IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create
5 chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

10 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion
15 can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will
20 not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

25

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAACTCACACATGCCCACC
GTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCG
30 TGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC
GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG

GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAA
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCG
5 CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC
GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGA
TGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

10

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degrees C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the

present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma
5 cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is
10 possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the
15 polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')₂ and other fragments of the antibodies of the present invention may be used according to the methods disclosed
20 herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

25 For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al.,
30 BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson

et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput

5 Screening Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described herein.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for
10 a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and
15 plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

20 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom
25 plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

30 Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates

of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degrees C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl_2 (anhyd); 0.00130 mg/L $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$; 0.050 mg/L of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$; 0.417 mg/L of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$; 311.80 mg/L of KCl; 28.64 mg/L of MgCl_2 ; 48.84 mg/L of MgSO_4 ; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO_3 ; 62.50 mg/L of $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$; 71.02 mg/L of Na_2HPO_4 ; .4320 mg/L of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine- H_2O ; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL- H_2O ; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL- H_2O ; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2 H_2O ; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed

with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

- 5 The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degrees C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

- 10 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

- 15 It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

- 20 One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

- 25 GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with
30 IL-12. Stat5 was originally called mammary growth factor, but has been found at

higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- α , IFN- γ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>JAKs</u>					<u>STATs</u>	<u>GAS(elements) or ISRE</u>
	<u>Ligand</u>	<u>tyk2</u>	<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	IL-10	+	?	?	-	1,3	
	<u>gp130 family</u>						
.0	IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	IL-11(Pleiotrophic)	?	+	?	?	1,3	
	OnM(Pleiotrophic)	?	+	+	?	1,3	
	LIF(Pleiotrophic)?	+	+	?	?	1,3	
	CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
.5	G-CSF(Pleiotrophic)	?	+	?	?	1,3	
	IL-12(Pleiotrophic)	+	-	+	+	1,3	
	<u>g-C family</u>						
10	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
15	IL-15	?	+	?	+	5	GAS
	<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
10	GM-CSF (myeloid)	-	-	+	-	5	GAS
	<u>Growth hormone family</u>						
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
15	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
	<u>Receptor Tyrosine Kinases</u>						
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCTCCCGAAATCTAGATTTCCTCCCGAAATGATTTCCTCCCGAAATGATTTCCTCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCTCCCGAAATCTAGATTTCCTCCCGAAATGATTTCCTCCCGAAATGATTTCCTCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGC
CGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGGCAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

25

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152),

30

although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4⁺ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-
5 SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is
10 demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life
15 Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25
20 flask and incubate at 37 degrees C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptides of the invention and/or induced polypeptides of
25 the invention as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100
30 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred
5 directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed
10 in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degrees C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4 degrees C and serve
15 as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as,
20 stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by determining
25 whether polypeptides of the invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

30 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and

wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing
5 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na₂HPO₄·7H₂O, 1 mM MgCl₂, and 675 uM CaCl₂. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degrees C for 36 hr.

10 The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described
15 growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37 degrees C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold
20 induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

25 When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

30 Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl

phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

5 The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

10 5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1
15 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

20 PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and
25 resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418
30 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count
5 the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR
10 can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

15 NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of
20 apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target
25 genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-KB would be useful in
30 treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

10 5':GCGGCAAGCTTTTGTCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

15 Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGC AAAAAGCTT:3' (SEQ ID NO:10)

25 Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

30 In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5

17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

5 Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes

in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small
5 molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for
10 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four
15 times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2.5×10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are
20 washed twice with HBSS, resuspended to 1×10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is
25 detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;
30 and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca⁺⁺ concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of
5 transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine
Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth
factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies.
In addition there are a large family of RPTKs for which the corresponding ligand is
unknown. Ligands for RPTKs include mainly secreted small proteins, but also
10 membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor
dimerization, resulting in transphosphorylation of the receptor subunits and activation
of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include
receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and
15 non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family,
members of which mediate signal transduction triggered by the cytokine superfamily
of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine
kinase activity, the identification of novel human secreted proteins capable of
20 activating tyrosine kinase signal transduction pathways are of interest. Therefore, the
following protocol is designed to identify those novel human secreted proteins
capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately
25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from
25 Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with
100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr
with 100 µl of cell culture grade type I collagen (50 µg/ml), gelatin (2%) or
polylysine (50 µg/ml), all of which can be purchased from Sigma Chemicals (St.
Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or
30 calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is
assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of
cell number through use of alamarBlue as described by the manufacturer Alamar

Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

- 5 To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM
- 10 HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4 degrees C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane
- 15 bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degrees C at 16,000 x g.
- 20 Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a
- 25 biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

- The tyrosine kinase reaction is set up by adding the following components in
- 30 order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride,

pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degrees C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

- 5 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degrees C for 20 min. This allows the streptavidin coated 96 well plate to associate with the
10 biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degrees C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and
15 incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

20 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be
25 used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by
30 substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are

then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any
5 of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degrees C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the
10 supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)
15 antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased
20 fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene
Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a
25 phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C,
30 using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre

Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

5 PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

 Genomic rearrangements are also observed as a method of determining
10 alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the
15 corresponding genomic locus.

 Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera
20 (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and
25 translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

30 A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus,

it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with
5 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample
10 containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature.
15 The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard
20 curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

25 **Example 23: Formulation**

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a
Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the
30 invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray.

"Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to

modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable
5 polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP
10 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers* 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *Id.*) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

15 Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see generally*, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317-327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE
20 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. (USA)* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than
25 about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see Langer, supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J.*
30 *Med.* 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes

(e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis.

Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered
5 separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be
10 administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently;
15 or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given
20 first, followed by the second.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the
25 Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™
30 (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the

invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in
5 any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott); COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott);
10 dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead);
15 DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β -L-FD4C and β -L-FddC (WO 98/17281).

20 Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn);
25 DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and
30 Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myers Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Wellcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine receptor agonists such as RANTES, SDF-1, MIP-1 α , MIP-1 β , etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compounds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide

reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1 α , MIP-1 β , SDF-1 α , IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN- α 2a; antagonists of TNFs, NF κ B, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al.*, *PNAS* 94:11567-72 (1997); Chen *et al.*, *Nat. Med.* 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF- α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α -naphthoflavone (WO 98/30213); and antioxidants such as γ -L-glutamyl-L-cysteine ethyl ester (γ -GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

- 5 In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, 10 RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ 15 (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any 20 combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or 25 prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with 30 FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another

specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with

5 PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

10 In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, 15 fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may 20 be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the 25 Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® 30 (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as

DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

5 In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™
10 (antithymocyte globulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In certain embodiments, the Therapeutics of the invention are administered
15 alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal,
20 etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid
25 derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

30 In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but

are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen
5 Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

10 Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate
15 including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten
20 oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum
25 (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the
30 context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated

Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydropoline, Thiaproline, alpha, alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; 5 Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium 10 Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase 15 inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 20 (1999)); carboxynaminolimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; 25 Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

30 Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the

function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

25 In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

30 In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is

contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or
5 polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth
10 factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be
15 administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan),
20 nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and
25 Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for
30 example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example,

Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone propionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing hormone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further

embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

5 In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more
10 radisotopes. Particularly preferred isotopes are ⁹⁰Y and ¹¹¹In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-
15 alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in
20 combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma
25 (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No.
30 WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202),

312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor

(GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amiodarone, bretylium, digitalis, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorophenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, triparamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I , radioactive isotopes of iodine such as ^{131}I and ^{123}I ; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth

- hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and
- 5 METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing
- 10 hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T₄™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T₃™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-
- 15 *n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca²⁺ channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).
- 20 Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or conjugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™
- 25 (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™
- 30 (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and

AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone),
5 LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-
10 NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders
15 include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™
20 and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotrophic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids
25 and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE
30 SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and

- VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate),
- 5 HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON
- 10 LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and
- 15 FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate),
- 20 DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and
- 25 ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone).

- Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof;
- 30 insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™;

oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (glyclazide), GLUCOPHAGE™ (metformin), PRECOSE™ (acarbose), AMARYL™ (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA™ (rosiglitazone maleate) ACTOS™ (pioglitazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® (progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B₁₂, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin,

folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that
5 may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine,
10 divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety
15 agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents
20 that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g.,
25 levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benzotropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents.
30 Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat,

fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

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Example 24: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically

effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy-Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and

initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is
5 maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue
10 culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

15 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the
20 media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is
25 produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

30 **Example 27: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention**

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a

promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the
5 activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous
10 polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends.
15 Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested
20 with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol
25 precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are
30 known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide

sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂ HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3X10⁶ cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately 1.5X10⁶ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V, respectively. As voltage increases, cell survival decreases, but

the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 28: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present
5 invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are
10 preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies
15 have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder,
20 stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It
25 is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery
30 and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express

polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA

in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked
5 DNA.

Example 29: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters,
10 guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

15 Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology
20 (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the
25 polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229
30 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into

enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

5 The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

25 Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also

30

be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

Example 30: Knock-Out Animals.

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene

of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & 5 Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered 10 to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, 15 muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the 20 transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The 25 engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; 30 genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and

Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

Example 31: Production of an Antibody

Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide(s) of the invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide(s) of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide(s) of the invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide(s) of the invention, or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10

g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide(s) of the invention.

Alternatively, additional antibodies capable of binding polypeptide(s) of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide(s) of the invention protein-specific antibody can be blocked by polypeptide(s) of the invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide(s) of the invention protein-specific antibody and are used to immunize an animal to induce formation of further polypeptide(s) of the invention protein-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

*Isolation Of Antibody Fragments Directed polypeptide(s) of the invention
From A Library Of scFvs*

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide(s) of the invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10⁹ E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10⁸ TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 32: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

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Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may

impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Purified polypeptides of the invention, or truncated forms thereof, is assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the polypeptides of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5×10^{-5} M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of

SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer
5 only, or 2 mg/Kg of a polypeptide of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with polypeptides of the invention identify the results of the activity of the polypeptides on spleen cells, such as the diffusion of peri-
10 arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell
15 representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with polypeptide is used to indicate whether the polypeptide specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

20 Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and polypeptide-treated mice.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to
25 test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

Example 33: T Cell Proliferation Assay

Proliferation assay for Resting PBLs.

30 A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ³H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control

mAb (B33.1) overnight at 4 °C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5×10^4 /well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of TNF Delta and/or TNF Epsilon protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 °C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored -20 °C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.4 microcuries of ^3H -thymidine and cultured at 37 °C for 18-24 hr. Wells are harvested and incorporation of ^3H -thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of TNF Delta and/or TNF Epsilon proteins.

Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of ^3H -thymidine. The assay is performed as follows. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200 microliters. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2 (*), IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants, recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 100ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ^3H -thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^3H -thymidine is used as a measure of

proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

(*) The amount of the control cytokines IL-2, IFN , TNF and IL-10 produced in each transfection varies between 300pg to 5ng/ml.

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Costimulation assay.

A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule. B7-1 expressed on activated APCs, results in enhancement of T cell responses including cell survival and production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

The assay is performed as follows. Ninety-six well plates are coated with 100ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 100ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution,

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therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFN , TNF , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ³H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ³H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

Costimulation assay: IFN γ and IL-2 ELISA

The assay is performed as follows. Twenty-four well plates are coated with either 300ng/ml or 600ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 500ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the costimulation assay. The assay is performed in the pre-coated twenty-four well plate using 1×10^5 cells/well in a final volume of 900ul. The supernatants (293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 300ul are added to 600ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only(negative control), IL-2, IFN , IL-12 and IL-18. In addition to the control supernatants recombinant human IL-2 (all cytokines were purchased from R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml, IL-12 at a final concentration of 1ng/ml and IL-18 at a final concentration of 50ng/ml are also used. Controls and unknown samples are tested in duplicate. Supernatant samples (250ul) are collected 2 days and 5 days after the beginning of the

assay. ELISAs to test for IFN and IL-2 secretion are performed using kits purchased from R & D Systems, (Minneapolis, MN). Results are expressed as an average of duplicate samples plus or minus standard error.

5 **Proliferation assay for preactivated-resting T cells.**

A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then
10 cultured in the presence of low doses of IL-2 resemble effector T cells. These cells are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of cells might enable
15 to detect the effect of very low doses of an unknown growth factor, that would not be sufficient to induce proliferation on resting (naïve) T cells.

The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in 10% FCS (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD) in the
20 presence of 2 µg/ml PHA (Sigma, Saint Louis, MO) for three days. The cells are then washed in PBS and cultured in 10% FCS/RPMI in the presence of 5 ng/ml of human recombinant IL-2 (R & D Systems, Minneapolis, MN) for 3 days. The cells are washed and rested in starvation medium (1% FCS/RPMI) for 16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to
25 determine the percentage of T cells (CD3 positive cells) present; this usually ranges between 93-97% depending on the donor. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200 µl. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60 µl are added to 140 µl of in 10% FCS/RPMI containing the cells. Control
30 supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2, IFN , TNF , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10 ng/ml is

also used. After 24 hours of culture, each well is pulsed with 1uCi of ^3H -thymidine(Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^3H -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

- 5 The studies described in this example test activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

10 **Example 34: Effect of Polypeptides of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells**

- 15 Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- α , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC γ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

- 20 FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

- 30 **Effect on the production of cytokines.** Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune

response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ($10^6/\text{ml}$) are treated with increasing concentrations of polypeptides of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell
5 cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion
10 molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation.
15 Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium
20 azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that
25 activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Polypeptides, agonists, or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral
30 blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque

gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively
5 lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free
10 medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2×10^6 /ml in PBS containing PI at a final concentration of 5 µg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA
15 fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is
20 performed as follows. Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of the a polypeptide of the invention and under the same conditions, but in the absence of the polypeptide. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of a polypeptide of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h
25 and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at 2×10^5
30 cell/well. Increasing concentrations of polypeptides of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is

removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H₂O₂ produced by the macrophages, a standard curve of a H₂O₂ solution of known molarity is performed for each experiment.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polypeptides, polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 35: Biological Effects of Polypeptides of the Invention

Astrocyte and Neuronal Assays

Recombinant polypeptides of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate a polypeptide of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of a polypeptide of the invention to

induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays

5 Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated
10 for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE₂ assays, the human lung fibroblasts are cultured at
15 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or polypeptides of the invention with or without IL-1 α for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to
20 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without polypeptides of the invention IL-1 α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or polypeptides of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth
25 of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with polypeptides of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of
30 striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic

projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP⁺) and released.

5 Subsequently, MPP⁺ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP⁺ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

10 It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, polypeptides of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential
20 effect of a polypeptide of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium
25 containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

30 Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons

would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a polypeptide of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the polypeptide may be involved in Parkinson's Disease.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 36: The Effect of Polypeptides of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at $2-5 \times 10^4$ cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. A polypeptide having the amino acid sequence of SEQ ID NO:Y, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the polypeptide of the invention may proliferate vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 37: Stimulatory Effect of Polypeptides of the Invention on the Proliferation of Vascular Endothelial Cells

For evaluation of mitogenic activity of growth factors, the colorimetric MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium) assay with the electron coupling reagent PMS (phenazine methosulfate) was

performed (CellTiter 96 AQ, Promega). Cells are seeded in a 96-well plate (5,000 cells/well) in 0.1 mL serum-supplemented medium and are allowed to attach overnight. After serum-starvation for 12 hours in 0.5% FBS, conditions (bFGF, VEGF₁₆₅ or a polypeptide of the invention in 0.5% FBS) with or without Heparin (8 U/ml) are added to wells for 48 hours. 20 mg of MTS/PMS mixture (1:0.05) are added per well and allowed to incubate for 1 hour at 37°C before measuring the absorbance at 490 nm in an ELISA plate reader. Background absorbance from control wells (some media, no cells) is subtracted, and seven wells are performed in parallel for each condition. See, Leak *et al. In Vitro Cell. Dev. Biol.* 30A:512-518 (1994).

10 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

15 **Example 38: Inhibition of PDGF-induced Vascular Smooth Muscle Cell Proliferation Stimulatory Effect**

HAoSMC proliferation can be measured, for example, by BrdUrd incorporation. Briefly, subconfluent, quiescent cells grown on the 4-chamber slides are transfected with CRP or FITC-labeled AT2-3LP. Then, the cells are pulsed with 10% calf serum and 6 mg/ml BrdUrd. After 24 h, immunocytochemistry is performed by using BrdUrd Staining Kit (Zymed Laboratories). In brief, the cells are incubated with the biotinylated mouse anti-BrdUrd antibody at 4 degrees C for 2 h after being exposed to denaturing solution and then incubated with the streptavidin-peroxidase and diaminobenzidine. After counterstaining with hematoxylin, the cells are mounted for microscopic examination, and the BrdUrd-positive cells are counted. The BrdUrd index is calculated as a percent of the BrdUrd-positive cells to the total cell number. In addition, the simultaneous detection of the BrdUrd staining (nucleus) and the FITC uptake (cytoplasm) is performed for individual cells by the concomitant use of bright field illumination and dark field-UV fluorescent illumination. See, Hayashida *et al.*, J. Biol. Chem. 6:271(36):21985-21992 (1996).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

Example 39: Stimulation of Endothelial Migration

This example will be used to explore the possibility that a polypeptide of the invention may stimulate lymphatic endothelial cell migration.

10 Endothelial cell migration assays are performed using a 48 well microchemotaxis chamber (Neuroprobe Inc., Cabin John, MD; Falk, W., et al., J. Immunological Methods 1980;33:239-247). Polyvinylpyrrolidone-free polycarbonate filters with a pore size of 8 um (Nucleopore Corp. Cambridge, MA) are coated with 0.1% gelatin for at least 6 hours at room temperature and dried under sterile air. Test substances are diluted to appropriate
15 concentrations in M199 supplemented with 0.25% bovine serum albumin (BSA), and 25 ul of the final dilution is placed in the lower chamber of the modified Boyden apparatus. Subconfluent, early passage (2-6) HUVEC or BMEC cultures are washed and trypsinized for the minimum time required to achieve cell detachment. After placing the filter between lower and upper chamber, 2.5×10^5 cells suspended in 50 ul M199 containing 1%
20 FBS are seeded in the upper compartment. The apparatus is then incubated for 5 hours at 37°C in a humidified chamber with 5% CO₂ to allow cell migration. After the incubation period, the filter is removed and the upper side of the filter with the non-migrated cells is scraped with a rubber policeman. The filters are fixed with methanol and stained with a Giemsa solution (Diff-Quick, Baxter, McGraw Park, IL). Migration is quantified by
25 counting cells of three random high-power fields (40x) in each well, and all groups are performed in quadruplicate.

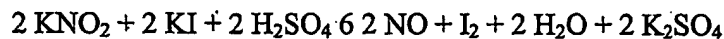
The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
30 invention.

Example 40: Stimulation of Nitric Oxide Production by Endothelial Cells

Nitric oxide released by the vascular endothelium is believed to be a mediator of vascular endothelium relaxation. Thus, activity of a polypeptide of the invention can be
 5 assayed by determining nitric oxide production by endothelial cells in response to the polypeptide.

Nitric oxide is measured in 96-well plates of confluent microvascular endothelial cells after 24 hours starvation and a subsequent 4 hr exposure to various levels of a positive control (such as VEGF-1) and the polypeptide of the invention. Nitric oxide in
 10 the medium is determined by use of the Griess reagent to measure total nitrite after reduction of nitric oxide-derived nitrate by nitrate reductase. The effect of the polypeptide of the invention on nitric oxide release is examined on HUVEC.

Briefly, NO release from cultured HUVEC monolayer is measured with a NO-specific polarographic electrode connected to a NO meter (Iso-NO, World Precision
 15 Instruments Inc.) (1049). Calibration of the NO elements is performed according to the following equation:



The standard calibration curve is obtained by adding graded concentrations of KNO_2 (0, 5, 10, 25, 50, 100, 250, and 500 nmol/L) into the calibration solution containing
 20 KI and H_2SO_4 . The specificity of the Iso-NO electrode to NO is previously determined by measurement of NO from authentic NO gas (1050). The culture medium is removed and HUVECs are washed twice with Dulbecco's phosphate buffered saline. The cells are then bathed in 5 ml of filtered Krebs-Henseleit solution in 6-well plates, and the cell plates are kept on a slide warmer (Lab Line Instruments Inc.) To maintain the temperature at 37°C.
 25 The NO sensor probe is inserted vertically into the wells, keeping the tip of the electrode 2 mm under the surface of the solution, before addition of the different conditions.

S-nitroso acetyl penicillamin (SNAP) is used as a positive control. The amount of released NO is expressed as picomoles per 1×10^6 endothelial cells. All values reported are means of four to six measurements in each group (number of cell culture wells). See,
 30 Leak *et al. Biochem. and Biophys. Res. Comm.* 217:96-105 (1995).

The studies described in this example tested activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to

test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5 **Example 41: Effect of Polypeptides of the Invention on Cord Formation in Angiogenesis**

Another step in angiogenesis is cord formation, marked by differentiation of endothelial cells. This bioassay measures the ability of microvascular endothelial cells to form capillary-like structures (hollow structures) when cultured *in vitro*.

10 CADMEC (microvascular endothelial cells) are purchased from Cell Applications, Inc. as proliferating (passage 2) cells and are cultured in Cell Applications' CADMEC Growth Medium and used at passage 5. For the *in vitro* angiogenesis assay, the wells of a 48-well cell culture plate are coated with Cell Applications' Attachment Factor Medium (200 ml/well) for 30 min. at 37°C. CADMEC are seeded onto the coated wells at 7,500
15 cells/well and cultured overnight in Growth Medium. The Growth Medium is then replaced with 300 mg Cell Applications' Chord Formation Medium containing control buffer or a polypeptide of the invention (0.1 to 100 ng/ml) and the cells are cultured for an additional 48 hr. The numbers and lengths of the capillary-like chords are quantitated through use of the Boeckeler VIA-170 video image analyzer. All assays are done in
20 triplicate.

Commercial (R&D) VEGF (50 ng/ml) is used as a positive control. b-esteradiol (1 ng/ml) is used as a negative control. The appropriate buffer (without protein) is also utilized as a control.

25 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

30 **Example 42: Angiogenic Effect on Chick Chorioallantoic Membrane**

Chick chorioallantoic membrane (CAM) is a well-established system to examine angiogenesis. Blood vessel formation on CAM is easily visible and quantifiable. The

ability of polypeptides of the invention to stimulate angiogenesis in CAM can be examined.

Fertilized eggs of the White Leghorn chick (*Gallus gallus*) and the Japanese quail (*Coturnix coturnix*) are incubated at 37.8°C and 80% humidity. Differentiated CAM of
5 16-day-old chick and 13-day-old quail embryos is studied with the following methods.

On Day 4 of development, a window is made into the egg shell of chick eggs. The embryos are checked for normal development and the eggs sealed with cellotape. They are further incubated until Day 13. Thermanox coverslips (Nunc, Naperville, IL) are cut into disks of about 5 mm in diameter. Sterile and salt-free growth factors are dissolved in
10 distilled water and about 3.3 mg/ 5 ml are pipetted on the disks. After air-drying, the inverted disks are applied on CAM. After 3 days, the specimens are fixed in 3% glutaraldehyde and 2% formaldehyde and rinsed in 0.12 M sodium cacodylate buffer. They are photographed with a stereo microscope [Wild M8] and embedded for semi- and ultrathin sectioning as described above. Controls are performed with carrier disks alone.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

20 **Example 43: Angiogenesis Assay Using a Matrigel Implant in Mouse**

In vivo angiogenesis assay of a polypeptide of the invention measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). The protein is mixed with the liquid Matrigel at 4
25 degree C and the mixture is then injected subcutaneously in mice where it solidifies. After 7 days, the solid "plug" of Matrigel is removed and examined for the presence of new blood vessels. Matrigel is purchased from Becton Dickinson Labware/Collaborative Biomedical Products.

When thawed at 4 degree C the Matrigel material is a liquid. The Matrigel is
30 mixed with a polypeptide of the invention at 150 ng/ml at 4 degrees C and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old are injected with the

mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue is removed). Replicate whole plugs are fixed in neutral buffered 10% formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug are processed. Selected sections are stained for the presence of vWF. The positive control for this assay is bovine basic FGF (150 ng/ml). Matrigel alone is used to determine basal levels of angiogenesis.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 44: Rescue of Ischemia in Rabbit Lower Limb Model

To study the in vivo effects of polynucleotides and polypeptides of the invention on ischemia, a rabbit hindlimb ischemia model is created by surgical removal of one femoral arteries as described previously (Takeshita *et al.*, *Am J. Pathol* 147:1649-1660 (1995)). The excision of the femoral artery results in retrograde propagation of thrombus and occlusion of the external iliac artery. Consequently, blood flow to the ischemic limb is dependent upon collateral vessels originating from the internal iliac artery (Takeshita *et al.* *Am J. Pathol* 147:1649-1660 (1995)). An interval of 10 days is allowed for post-operative recovery of rabbits and development of endogenous collateral vessels. At 10 day post-operatively (day 0), after performing a baseline angiogram, the internal iliac artery of the ischemic limb is transfected with 500 mg naked expression plasmid containing a polynucleotide of the invention by arterial gene transfer technology using a hydrogel-coated balloon catheter as described (Riessen *et al.* *Hum Gene Ther.* 4:749-758 (1993); Leclerc *et al.* *J. Clin. Invest.* 90: 936-944 (1992)). When a polypeptide of the invention is used in the treatment, a single bolus of 500 mg polypeptide of the invention or control is delivered into the internal iliac artery of the ischemic limb over a period of 1

min. through an infusion catheter. On day 30, various parameters are measured in these rabbits: (a) BP ratio - The blood pressure ratio of systolic pressure of the ischemic limb to that of normal limb; (b) Blood Flow and Flow Reserve - Resting FL: the blood flow during undilated condition and Max FL: the blood flow during fully dilated condition (also an indirect measure of the blood vessel amount) and Flow Reserve is reflected by the ratio of max FL: resting FL; (c) Angiographic Score - This is measured by the angiogram of collateral vessels. A score is determined by the percentage of circles in an overlaying grid that with crossing opacified arteries divided by the total number in the rabbit thigh; (d) Capillary density - The number of collateral capillaries determined in light microscopic sections taken from hindlimbs.

The studies described in this example tested activity of polynucleotides and polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the agonists, and/or antagonists of the invention.

15 **Example 45: Effect of Polypeptides of the Invention on Vasodilation**

Since dilation of vascular endothelium is important in reducing blood pressure, the ability of polypeptides of the invention to affect the blood pressure in spontaneously hypertensive rats (SHR) is examined. Increasing doses (0, 10, 30, 100, 300, and 900 mg/kg) of the polypeptides of the invention are administered to 13-14 week old spontaneously hypertensive rats (SHR). Data are expressed as the mean +/- SEM. Statistical analysis are performed with a paired t-test and statistical significance is defined as $p < 0.05$ vs. the response to buffer alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

30 **Example 46: Rat Ischemic Skin Flap Model**

The evaluation parameters include skin blood flow, skin temperature, and factor VIII immunohistochemistry or endothelial alkaline phosphatase reaction. Expression of

polypeptides of the invention, during the skin ischemia, is studied using in situ hybridization.

The study in this model is divided into three parts as follows:

Ischemic skin

5 Ischemic skin wounds

Normal wounds

The experimental protocol includes:

Raising a 3x4 cm, single pedicle full-thickness random skin flap (myocutaneous flap over the lower back of the animal).

10 An excisional wounding (4-6 mm in diameter) in the ischemic skin (skin-flap).

Topical treatment with a polypeptide of the invention of the excisional wounds (day 0, 1, 2, 3, 4 post-wounding) at the following various dosage ranges: 1mg to 100 mg.

Harvesting the wound tissues at day 3, 5, 7, 10, 14 and 21 post-wounding for histological, immunohistochemical, and in situ studies.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

20 **Example 47: Peripheral Arterial Disease Model**

Angiogenic therapy using a polypeptide of the invention is a novel therapeutic strategy to obtain restoration of blood flow around the ischemia in case of peripheral arterial diseases. The experimental protocol includes:

25 One side of the femoral artery is ligated to create ischemic muscle of the hindlimb, the other side of hindlimb serves as a control.

a polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-3 weeks.

The ischemic muscle tissue is collected after ligation of the femoral
30 artery at 1, 2, and 3 weeks for the analysis of expression of a polypeptide of the invention and histology. Biopsy is also performed on the other side of normal muscle of the contralateral hindlimb.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

Example 48: Ischemic Myocardial Disease Model

A polypeptide of the invention is evaluated as a potent mitogen capable of stimulating the development of collateral vessels, and restructuring new vessels after
10 coronary artery occlusion. Alteration of expression of the polypeptide is investigated in situ. The experimental protocol includes:

The heart is exposed through a left-side thoracotomy in the rat. Immediately, the left coronary artery is occluded with a thin suture (6-0) and the thorax is closed.

a polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered
15 intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-4 weeks.

Thirty days after the surgery, the heart is removed and cross-sectioned for morphometric and in situ analyzes.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to
20 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 49: Rat Corneal Wound Healing Model

25 This animal model shows the effect of a polypeptide of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

Inserting a spatula below the lip of the incision facing the outer corner of the eye.

Making a pocket (its base is 1-1.5 mm from the edge of the eye).

30 Positioning a pellet, containing 50ng- 5ug of a polypeptide of the invention, within the pocket.

Treatment with a polypeptide of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to
5 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 50: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

10

Diabetic db+/db+ Mouse Model.

To demonstrate that a polypeptide of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and
15 reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II
20 diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin
25 levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.*
30 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These

homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

A polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

- 5 Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post
10 treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

- 15 Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by
20 treatment with a polypeptide of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

- 25 Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

- 30 Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer can serve as a positive tissue control and human brain tissue can be used as a negative tissue control. Each specimen includes a section with omission of the primary

antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is
5 considered significant.

Steroid Impaired Rat Model

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-
10 Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*,
15 *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth*
20 *Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that a polypeptide of the invention can accelerate the healing
25 process, the effects of multiple topical applications of the polypeptide on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and
30 are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad*

libitum. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

5 The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue
10 punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

 Wounds are visually examined and photographed at a fixed distance at the day of
15 wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

 The polypeptide of the invention is administered using at a range different doses,
20 from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

 Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue
25 cassettes between biopsy sponges for further processing.

 Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

 Wound closure is analyzed by measuring the area in the vertical and horizontal
30 axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8).

The wound area on day 1 is 64mm^2 , the corresponding size of the dermal punch.

Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

5

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with a polypeptide of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

10

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

15

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

20

Example 51: Lymphadema Animal Model

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of a polypeptide of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

25

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing.

30

Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of
5 dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main
10 lymphatic vessels in this area are then electrically coagulated suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose
15 tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying
20 muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated
25 places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb
30 movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then
5 dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca²⁺ comparison.

10 Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee
15 (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics...

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to
20 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 52: Suppression of TNF alpha-induced adhesion molecule
expression by a Polypeptide of the Invention**

25 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and
30 endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and

extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

5 Tumor necrosis factor alpha (TNF- α), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of a polypeptide of the invention to mediate a suppression of TNF- α induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- α treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO₂.

15 HUVECs are seeded in 96-well plates at concentrations of 1×10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 μ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution

of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with
5 PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is
10 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [
15 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
20 invention.

Example 53: Assay for the Stimulation of Bone Marrow CD34+ Cell

Proliferation

This assay is based on the ability of human CD34+ to proliferate in the
25 presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range
30 of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone

has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, 100 μ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μ l of prepared cytokines, 50 μ l SID (supernatants at 1:2 dilution = 50 μ l) and 20 μ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 μ l. The plates are then placed in a 37°C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μ Ci/well of [3H] Thymidine is added in a 10 μ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined

via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34⁺ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34⁺ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 54: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5\beta_1$ and $\alpha_4\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The

factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

- Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with
5 fn fragment at a coating concentration of $0.2 \mu\text{g}/\text{cm}^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products are tested with appropriate negative controls in
10 the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2 , 7% O_2 , and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA.
15 Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

- One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or
20 antagonists and fragments and variants thereof.

- If a particular gene product is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and
25 "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

- Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the
30 proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses

of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 55: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF α stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μ g/ml hEGF, 5mg/ml insulin, 1 μ g/ml hFGF, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 5%FBS. After incubation @ 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for

AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed which should always include media controls and known-protein controls.

- 5 For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Then add 1/3 vol media containing controls or supernatants and incubate at 37C/5% CO₂ until day 5.

- 10 Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

- 15 On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 µl/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

- On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of
20 Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

- 25 Wash plates with wash buffer and blot on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Wash plates with wash buffer. Blot on paper towels.

- Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each
30 assay were tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the gene product of interest may be involved in dermal fibroblast proliferation and/or

smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the gene/gene product of interest. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the gene product and polynucleotides of the gene may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 56: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of

the ExtraAvidin-Alkaline Phosphatase in glycine buffer: $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$. 5 μ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNPN reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 57: Alamar Blue Endothelial Cells Proliferation Assay

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The

plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 58: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml,

Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to
5 wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration
10 of 10 μ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 μ C of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and
15 compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or
20 antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

25 The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both
30 incorporated herein by reference in their entireties. Additionally, the specifications and sequence listings of U.S. Provisional Applications Serial Nos. 60/184,836 and 60/193,170 are all hereby incorporated by reference in their entirety.

Table 3

(Gene No: 30 / Clone ID: HTPBW79)

	Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met 1	.	.	B	B	.	.	.	-0.37	0.07	*	*	.	-0.30	0.86
	Arg 2	.	.	B	B	.	.	.	0.02	0.43	*	*	.	-0.60	0.59
	Thr 3	.	.	B	B	.	.	.	-0.40	0.40	*	*	.	-0.30	0.74
	Leu 4	A	A	-0.82	0.66	*	*	.	-0.60	0.61
10	Phe 5	A	A	-0.72	0.73	*	*	.	-0.60	0.26
	Asn 6	A	A	-0.93	1.64	*	*	.	-0.60	0.19
	Leu 7	A	A	-1.63	1.84	*	*	.	-0.60	0.19
	Leu 8	A	A	-2.13	1.66	.	.	.	-0.60	0.22
	Trp 9	A	A	-1.91	1.56	.	.	.	-0.60	0.11
15	Leu 10	A	A	-1.88	1.66	.	.	.	-0.60	0.14
	Ala 11	A	A	-2.18	1.54	.	.	.	-0.60	0.09
	Leu 12	A	A	-1.58	1.24	.	.	.	-0.60	0.11
	Ala 13	A	A	-1.62	0.76	.	.	.	-0.60	0.21
	Cys 14	.	A	B	-1.37	0.71	.	.	.	-0.60	0.16
20	Ser 15	.	A	B	-0.87	0.71	.	.	.	-0.60	0.26
	Pro 16	.	.	B	B	.	.	.	-0.59	0.51	.	.	.	-0.60	0.37
	Val 17	.	.	B	B	.	.	.	-0.59	0.50	.	.	.	-0.60	1.00
	His 18	.	.	B	B	.	.	.	-0.30	0.61	*	.	F	-0.45	0.61
	Thr 19	.	.	B	B	.	.	.	0.41	0.61	*	.	F	-0.45	0.53
25	Thr 20	.	.	B	B	.	.	.	0.41	0.19	.	.	F	0.00	1.44
	Leu 21	A	.	.	B	.	.	.	0.62	-0.07	.	.	F	0.60	1.41
	Ser 22	A	T	.	0.89	-0.57	.	*	F	1.30	1.64
	Lys 23	A	T	.	0.97	-0.56	.	.	F	1.30	1.15
	Ser 24	A	T	.	1.32	-1.04	.	.	F	1.30	2.78
30	Asp 25	A	T	.	1.04	-1.73	.	.	F	1.30	4.15
	Ala 26	A	A	1.27	-1.61	.	.	F	0.90	2.09
	Lys 27	A	A	1.27	-1.11	*	.	F	0.90	1.58
	Lys 28	A	A	1.27	-1.11	*	*	F	0.90	1.27
	Ala 29	A	A	1.26	-1.11	*	.	F	0.90	2.51
35	Ala 30	A	A	0.44	-1.13	*	.	F	0.90	1.81
	Ser 31	A	A	0.22	-0.44	*	.	F	0.45	0.75
	Lys 32	A	A	0.18	0.24	.	.	F	-0.15	0.61
	Thr 33	A	A	0.18	-0.26	.	.	F	0.60	1.04
	Leu 34	A	A	0.47	-0.76	.	.	F	0.90	1.56
40	Leu 35	A	A	1.06	-0.76	.	.	F	0.90	1.04
	Glu 36	A	A	0.66	-0.36	.	.	F	0.60	1.25
	Lys 37	A	A	0.31	-0.06	.	.	F	0.94	1.32
	Ser 38	A	A	0.62	-0.36	.	*	F	1.28	2.14
	Gln 39	A	A	1.48	-1.04	.	*	F	1.92	2.06
45	Phe 40	T	T	.	2.08	-1.04	.	.	F	3.06	2.06
	Ser 41	T	T	.	1.22	-0.61	.	.	F	3.40	2.38
	Asp 42	T	T	.	1.18	-0.36	.	*	F	2.76	1.02
	Lys 43	T	C	1.48	-0.36	.	*	F	2.39	2.04
	Pro 44	C	1.59	-1.14	.	*	F	2.32	2.54
50	Val 45	.	.	B	1.94	-1.53	.	.	F	1.95	2.98
	Gln 46	.	.	B	1.43	-1.10	.	*	F	1.78	1.47
	Asp 47	.	.	B	.	.	T	.	0.58	-0.41	.	.	F	1.70	0.79
	Arg 48	.	.	B	.	.	T	.	-0.32	-0.20	.	.	F	1.53	0.79
	Gly 49	.	.	B	.	.	T	.	-0.42	-0.20	.	*	F	1.36	0.34
55	Leu 50	.	.	B	.	.	T	.	0.43	-0.11	.	*	.	1.04	0.29
	Val 51	.	.	B	B	.	.	.	-0.38	-0.11	.	*	.	0.47	0.25
	Val 52	.	.	B	B	.	.	.	-0.33	0.57	.	*	.	-0.60	0.21
	Thr 53	.	.	B	B	.	.	.	-1.03	0.14	.	*	F	-0.15	0.50
	Asp 54	A	.	.	B	.	.	.	-0.69	-0.04	.	*	F	0.45	0.68
60	Leu 55	A	A	-0.18	-0.69	.	*	F	0.90	1.59
	Lys 56	A	A	-0.18	-0.94	.	*	F	0.90	1.48
	Ala 57	A	A	-0.18	-0.79	.	*	F	0.75	0.66
	Glu 58	A	A	.	B	.	.	.	-0.68	-0.14	.	*	F	0.45	0.59

5	Ser	59	A	A	.	B	.	.	-0.68	-0.14	*	F	0.45	0.24
	Val	60	A	A	.	B	.	.	0.10	-0.14	*	.	0.30	0.42
	Val	61	A	A	.	B	.	.	0.17	-0.14	*	.	0.30	0.33
	Leu	62	A	A	.	B	.	.	0.46	-0.14	*	.	0.30	0.48
	Glu	63	A	A	.	B	.	.	0.21	-0.14	*	.	0.30	0.87
	His	64	A	T	-0.16	-0.03	*	.	0.85	1.83
	Arg	65	A	T	0.40	-0.10	*	.	0.85	1.19
	Ser	66	A	T	0.67	-0.40	*	.	0.70	0.92
10	Tyr	67	A	T	1.52	0.10	*	.	0.10	0.68
	Cys	68	A	A	0.93	-0.40	*	.	0.30	0.70
	Ser	69	A	A	1.08	0.10	*	.	-0.30	0.53
	Ala	70	A	A	0.97	-0.29	*	.	0.30	0.66
	Lys	71	A	A	1.38	-1.04	*	F	0.90	2.05
	Ala	72	A	A	1.59	-1.61	*	F	0.90	3.00
15	Arg	73	A	A	1.56	-1.50	*	F	0.90	4.04
	Asp	74	A	A	1.27	-1.21	*	F	0.90	1.75
	Arg	75	A	A	1.51	-0.71	*	.	0.75	1.75
	His	76	.	A	B	.	.	.	1.47	-0.79	*	.	0.60	0.88
20	Phe	77	.	A	B	.	.	.	1.20	-0.79	*	.	0.60	0.88
	Ala	78	.	A	B	.	.	.	0.28	-0.14	*	.	0.30	0.33
	Gly	79	.	.	B	B	.	.	-0.07	0.54	.	.	-0.60	0.20
	Asp	80	.	.	.	B	T	.	-0.42	0.47	*	.	-0.20	0.23
	Val	81	.	.	B	B	.	.	-1.24	0.44	*	.	-0.60	0.36
25	Leu	82	.	.	B	B	.	.	-0.86	0.59	*	.	-0.60	0.27
	Gly	83	.	.	B	B	.	.	-0.48	0.64	.	.	-0.60	0.23
	Tyr	84	.	.	B	B	.	.	-0.42	1.07	.	.	-0.60	0.49
	Val	85	.	.	B	B	.	.	-0.42	1.34	.	.	-0.60	0.62
	Thr	86	.	.	B	B	.	.	0.13	1.06	.	.	-0.45	1.01
30	Pro	87	.	.	B	B	.	.	0.91	1.01	.	F	-0.45	0.86
	Trp	88	T	.	0.91	0.76	.	F	0.30	1.58
	Asn	89	T	0.91	0.54	.	F	0.30	1.08
	Ser	90	T	1.77	0.81	*	.	0.15	1.10
	His	91	T	1.22	0.39	.	.	0.45	1.74
35	Gly	92	T	T	1.12	0.11	*	.	0.50	0.80
	Tyr	93	.	.	.	B	T	.	1.46	0.20	*	.	0.10	0.87
	Asp	94	.	.	B	B	.	.	0.60	-0.19	*	.	0.45	1.27
	Val	95	.	.	B	B	.	.	0.20	-0.04	*	.	0.30	0.95
	Thr	96	.	.	B	B	.	.	-0.11	0.31	*	.	-0.30	0.53
40	Lys	97	.	.	B	B	.	.	-0.07	-0.01	*	F	0.45	0.31
	Val	98	.	.	B	B	.	.	0.22	0.37	*	F	-0.15	0.56
	Phe	99	.	.	B	B	.	.	-0.48	-0.27	*	F	0.45	0.78
	Gly	100	.	.	.	B	T	.	0.07	0.03	*	F	0.25	0.34
	Ser	101	.	.	B	B	.	.	0.38	0.51	*	F	-0.45	0.66
45	Lys	102	.	.	B	B	.	.	-0.56	0.27	*	F	0.00	1.32
	Phe	103	.	.	.	B	T	.	0.00	0.17	.	F	0.25	0.93
	Thr	104	.	.	B	B	.	.	0.49	0.13	*	F	-0.15	0.93
	Gln	105	.	.	B	B	.	.	-0.02	0.17	.	F	-0.15	0.72
	Ile	106	.	.	B	B	.	.	-0.01	0.81	.	F	-0.45	0.62
50	Ser	107	.	.	B	B	.	.	-0.87	0.94	*	F	-0.45	0.45
	Pro	108	.	.	B	B	.	.	-0.17	1.14	*	.	-0.60	0.21
	Val	109	.	A	B	B	.	.	-0.67	1.14	*	.	-0.60	0.53
	Trp	110	.	A	B	B	.	.	-0.62	1.14	*	.	-0.60	0.33
	Leu	111	.	A	B	B	.	.	0.38	0.76	*	*	-0.30	0.42
55	Gln	112	.	A	B	B	.	.	0.79	0.33	*	*	0.45	1.11
	Leu	113	.	A	B	B	.	.	0.66	-0.31	*	*	1.35	2.07
	Lys	114	.	A	.	B	.	C	1.62	-0.80	*	F	2.30	2.49
	Arg	115	T	C	1.91	-1.49	*	F	3.00	2.81
	Arg	116	T	C	2.12	-1.89	*	F	2.70	5.90
60	Gly	117	T	C	1.42	-1.96	*	F	2.40	2.92
	Arg	118	T	C	2.23	-1.17	*	F	2.10	1.29
	Glu	119	A	A	B	.	.	.	1.33	-1.17	*	.	1.05	1.14
	Met	120	A	A	.	B	.	.	0.91	-0.53	*	.	0.60	0.86
	Phe	121	A	A	.	B	.	.	0.46	-0.47	*	.	0.30	0.63

	Glu	122	A	A	.	B	.	.	.	-0.01	-0.04	.	*	.	0.30	0.36
	Val	123	A	A	.	B	.	.	.	-0.16	0.64	.	*	.	-0.60	0.30
	Thr	124	A	A	.	B	.	.	.	-0.16	0.53	.	.	.	-0.60	0.47
	Gly	125	A	A	.	B	.	.	.	-0.41	-0.26	.	*	.	0.30	0.46
5	Leu	126	A	.	.	B	.	.	.	0.29	0.39	.	*	.	-0.30	0.46
	His	127	A	.	.	B	.	.	.	0.29	-0.26	.	.	.	0.30	0.53
	Asp	128	A	0.80	-0.34	*	.	.	0.50	0.92
	Val	129	A	0.82	-0.34	*	.	F	0.80	1.11
	Asp	130	A	T	.	0.57	-0.11	*	.	F	0.85	0.86
10	Gln	131	A	T	.	1.49	0.00	*	.	F	0.25	0.51
	Gly	132	A	T	.	0.93	0.00	*	.	F	0.40	1.34
	Trp	133	A	T	.	0.08	-0.14	*	.	.	0.70	0.81
	Met	134	A	A	1.04	0.50	*	.	.	-0.60	0.35
	Arg	135	A	A	1.09	0.10	*	.	.	-0.30	0.69
15	Ala	136	A	A	1.06	-0.33	*	.	.	0.45	1.30
	Val	137	A	A	0.81	-0.74	*	*	.	0.75	1.79
	Arg	138	A	A	1.14	-0.86	*	*	.	0.60	0.93
	Lys	139	A	A	1.40	-0.86	*	.	F	0.90	1.83
	His	140	A	A	0.48	-0.93	*	.	F	0.90	2.44
20	Ala	141	A	A	1.03	-0.89	*	*	F	0.90	1.03
	Lys	142	A	A	1.00	-0.39	*	*	F	0.45	0.70
	Gly	143	.	A	B	0.03	0.30	*	.	.	-0.30	0.36
	Leu	144	.	A	B	-0.22	0.44	*	.	.	-0.60	0.26
	His	145	.	A	B	-0.08	0.37	*	*	.	-0.30	0.20
25	Ile	146	.	A	B	-0.30	0.37	*	*	.	-0.30	0.41
	Val	147	.	A	B	-1.16	0.63	*	*	.	-0.60	0.41
	Pro	148	.	A	B	-1.51	0.63	*	*	.	-0.60	0.25
	Arg	149	.	A	B	-0.70	0.91	*	*	.	-0.60	0.30
	Leu	150	.	A	B	-0.67	0.23	*	*	.	-0.30	0.71
30	Leu	151	.	A	B	-0.07	-0.41	*	*	.	0.30	0.76
	Phe	152	.	A	B	0.48	0.07	*	.	.	-0.30	0.41
	Glu	153	A	A	0.44	0.56	.	*	.	-0.60	0.72
	Asp	154	.	A	.	.	.	T	.	0.33	0.63	.	*	.	-0.05	1.37
	Trp	155	.	A	.	.	.	T	.	1.14	-0.06	.	.	.	1.19	2.63
35	Thr	156	A	A	1.26	-0.84	*	*	.	1.43	2.54
	Tyr	157	T	T	2.07	-0.06	*	.	.	2.27	1.32
	Asp	158	T	T	2.07	-0.06	*	.	F	2.76	2.45
	Asp	159	T	T	1.21	-0.57	*	.	F	3.40	2.73
	Phe	160	T	T	0.69	-0.41	*	*	F	2.76	1.29
40	Arg	161	.	.	B	B	.	.	.	1.00	-0.49	*	*	F	1.47	0.64
	Asn	162	.	.	B	B	.	.	.	0.94	-0.49	*	*	.	0.98	0.64
	Val	163	.	.	.	B	.	.	C	0.94	-0.10	*	*	.	0.84	0.99
	Leu	164	.	.	.	B	.	.	C	0.94	-0.89	*	*	F	0.95	0.87
	Asp	165	A	T	.	1.64	-0.89	*	*	F	1.15	0.91
45	Ser	166	A	T	.	0.64	-1.29	*	*	F	1.30	2.12
	Glu	167	A	T	.	0.64	-1.24	*	.	F	1.30	1.80
	Asp	168	A	T	.	1.50	-1.93	*	.	F	1.30	1.87
	Glu	169	A	A	1.50	-1.93	.	*	F	0.90	2.41
	Ile	170	A	A	1.20	-1.63	*	.	F	0.90	1.15
50	Glu	171	A	A	1.54	-1.24	*	.	F	0.75	0.92
	Glu	172	A	A	1.23	-1.24	*	.	F	0.90	1.07
	Leu	173	A	A	0.38	-0.76	*	.	F	0.90	2.19
	Ser	174	A	.	.	B	.	.	.	-0.48	-0.80	*	.	F	0.75	0.94
	Lys	175	A	.	.	B	.	.	.	0.41	-0.16	*	.	F	0.45	0.40
55	Thr	176	A	.	.	B	.	.	.	-0.44	0.24	*	.	F	-0.15	0.85
	Val	177	A	.	.	B	.	.	.	-1.03	0.20	*	.	.	-0.30	0.47
	Val	178	A	.	.	B	.	.	.	-0.18	0.31	*	.	.	-0.30	0.24
	Gln	179	A	.	.	B	.	.	.	0.12	0.31	*	.	.	-0.30	0.33
	Val	180	A	.	.	B	.	.	.	0.08	0.23	*	.	.	-0.30	0.71
60	Ala	181	.	.	B	B	.	.	.	0.36	-0.01	.	.	.	0.45	1.66
	Lys	182	A	.	.	B	.	.	.	0.51	-0.16	.	.	F	0.70	1.30
	Asn	183	.	.	B	1.37	0.23	.	.	F	0.40	1.52
	Gln	184	.	.	B	1.02	-0.41	.	.	F	1.10	2.51

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	His	185	T	C	1.18	-0.49	.	.	F	1.60	1.24
	Phe	186	T	T	.	0.91	0.30	.	.	.	1.00	0.67
	Asp	187	.	.	B	.	.	T	.	0.01	0.54	.	.	.	0.20	0.29
5	Gly	188	.	.	B	.	.	T	.	0.01	0.79	*	.	.	0.10	0.16
	Phe	189	.	.	B	B	.	.	.	-0.84	0.29	*	.	.	-0.10	0.31
	Val	190	.	.	B	B	.	.	.	-1.10	0.14	*	.	.	-0.20	0.14
	Val	191	.	.	B	B	.	.	.	-0.40	1.06	*	.	.	-0.60	0.15
	Glu	192	A	.	.	B	.	.	.	-0.40	1.03	*	.	.	-0.60	0.27
10	Val	193	A	.	.	B	.	.	.	-0.87	0.64	*	.	.	-0.60	0.64
	Trp	194	A	.	.	B	.	.	.	-0.98	0.69	*	.	.	-0.60	0.71
	Asn	195	A	.	.	B	.	.	.	-0.42	0.73	*	.	.	-0.60	0.34
	Gln	196	A	.	.	B	.	.	.	0.43	1.11	.	.	.	-0.60	0.61
	Leu	197	A	.	.	B	.	.	.	0.48	0.87	*	.	F	-0.30	1.01
15	Leu	198	A	.	.	B	.	.	.	1.44	-0.04	.	.	F	0.78	1.25
	Ser	199	.	.	.	B	.	.	C	0.88	-0.44	.	*	F	1.16	1.42
	Gln	200	.	.	.	B	T	.	.	0.57	-0.20	.	.	F	1.54	1.28
	Lys	201	.	.	B	B	.	.	.	0.57	-0.40	.	*	F	1.32	2.23
	Arg	202	.	.	B	B	.	.	.	1.38	-1.09	*	*	F	1.80	2.78
20	Val	203	.	.	B	B	.	.	.	1.38	-1.07	*	.	F	1.62	2.78
	Thr	204	.	.	B	B	.	.	.	1.33	-0.79	*	*	F	1.44	1.15
	Asp	205	.	.	B	.	.	T	.	0.73	-0.36	*	*	F	1.21	0.58
	Gln	206	A	T	.	-0.01	0.26	*	.	.	0.28	0.77
	Leu	207	A	T	.	-0.43	0.40	*	*	.	-0.20	0.46
25	Gly	208	A	T	.	0.39	0.40	*	.	.	-0.20	0.40
	Met	209	A	A	0.74	0.90	.	.	.	-0.60	0.31
	Phe	210	A	A	0.74	0.50	.	.	.	-0.60	0.76
	Thr	211	A	A	0.04	-0.19	*	.	.	0.45	1.34
30	His	212	A	A	0.86	0.17	.	.	.	-0.15	1.17
	Lys	213	A	A	1.20	-0.44	*	.	F	0.60	2.34
	Glu	214	A	A	0.99	-0.83	*	.	F	0.90	2.81
	Phe	215	A	A	1.10	-0.63	*	.	F	0.90	1.70
	Glu	216	A	A	1.20	-0.63	*	.	F	0.75	0.86
	Gln	217	A	A	0.38	-0.20	*	.	.	0.30	0.77
35	Leu	218	A	A	-0.48	0.44	*	.	.	-0.60	0.66
	Ala	219	A	A	-0.48	0.34	*	.	.	-0.30	0.31
	Pro	220	A	-0.12	0.34	*	.	.	-0.10	0.30
	Val	221	A	-0.82	0.37	*	.	.	-0.10	0.36
	Leu	222	A	-1.12	0.47	.	.	.	-0.40	0.31
40	Asp	223	A	T	.	-1.12	0.36	.	.	.	0.10	0.27
	Gly	224	.	.	B	.	.	T	.	-1.13	0.61	.	.	.	-0.20	0.30
	Phe	225	.	.	B	.	.	T	.	-1.23	0.59	.	.	.	-0.20	0.36
	Ser	226	.	.	B	.	.	T	.	-0.62	0.39	.	.	.	0.10	0.31
	Leu	227	.	.	B	0.19	1.14	.	.	.	-0.40	0.49
45	Met	228	.	.	B	-0.06	0.71	.	.	.	-0.40	0.95
	Thr	229	.	.	B	.	.	T	.	-0.01	0.69	.	.	.	-0.05	1.11
	Tyr	230	T	T	.	0.38	0.69	.	.	.	0.35	1.80
	Asp	231	T	T	.	0.09	0.49	.	.	.	0.35	2.62
	Tyr	232	T	T	.	0.87	0.37	.	.	.	0.65	1.84
50	Ser	233	.	.	B	1.47	0.39	.	.	.	0.05	1.59
	Thr	234	.	.	B	1.57	0.03	.	.	.	0.05	1.65
	Ala	235	.	.	B	1.47	0.46	.	.	.	-0.25	1.63
	His	236	.	.	B	1.26	0.13	.	.	F	0.20	1.21
	Gln	237	C	1.50	0.17	.	.	F	0.40	1.29
55	Pro	238	C	1.21	0.09	.	.	F	0.40	2.06
	Gly	239	T	C	1.31	0.09	.	.	F	0.60	1.53
	Pro	240	T	T	.	1.09	0.01	.	.	F	0.80	1.36
	Asn	241	T	C	0.82	0.30	.	*	F	0.45	0.73
	Ala	242	T	C	0.53	0.26	.	.	F	0.45	0.98
60	Pro	243	.	.	B	-0.11	0.74	*	.	.	-0.40	0.67
	Leu	244	.	.	B	B	.	.	.	0.34	0.96	*	.	.	-0.60	0.31
	Ser	245	.	.	B	B	.	.	.	-0.03	0.56	*	.	.	-0.60	0.60
	Trp	246	.	.	B	B	.	.	.	-0.70	0.56	*	*	.	-0.60	0.39
	Val	247	.	.	B	B	.	.	.	-0.97	0.70	*	*	.	-0.60	0.25

5	Arg	248	.	.	B	B	.	.	-0.76	0.66	*	*	.	-0.60	0.14
	Ala	249	.	.	B	B	.	.	-0.80	0.67	*	*	.	-0.60	0.23
	Cys	250	.	.	B	B	.	.	-1.31	0.40	*	*	.	-0.60	0.23
	Val	251	.	.	B	B	.	.	-1.02	0.44	*	*	.	-0.60	0.10
	Gln	252	.	.	B	B	.	.	-0.38	0.44	*	*	.	-0.60	0.16
	Val	253	.	.	B	B	.	.	-0.44	0.37	*	*	.	0.04	0.47
	Leu	254	.	.	B	B	.	.	-0.16	-0.20	.	*	.	1.13	1.25
	Asp	255	.	.	B	.	.	T	0.56	-0.46	.	*	F	1.87	0.97
10	Pro	256	T	T	1.12	-0.86	.	*	F	3.06	2.62
	Lys	257	T	T	1.23	-0.59	.	*	F	3.40	3.34
	Ser	258	A	T	1.79	-1.27	.	*	F	2.66	3.91
	Lys	259	A	2.64	-0.89	.	*	F	2.12	3.39
	Trp	260	A	T	1.76	-1.31	.	*	F	1.98	3.39
15	Arg	261	A	T	1.16	-0.63	.	*	F	1.64	1.77
	Ser	262	.	.	B	.	.	T	0.30	-0.33	.	*	F	0.85	0.73
	Lys	263	.	.	B	.	.	T	0.26	0.36	.	*	F	0.25	0.57
	Ile	264	.	.	B	B	.	.	-0.60	-0.13	.	*	.	0.30	0.29
	Leu	265	.	.	B	B	.	.	-0.31	0.56	.	*	.	-0.60	0.18
20	Leu	266	.	.	B	B	.	.	-1.12	0.57	.	*	.	-0.60	0.14
	Gly	267	.	.	B	B	.	.	-1.07	1.36	.	*	.	-0.60	0.18
	Leu	268	.	.	B	.	.	.	-1.46	1.43	.	*	.	-0.40	0.34
	Asn	269	.	.	B	.	.	.	-1.17	1.17	.	*	.	-0.40	0.40
	Phe	270	.	.	B	.	.	.	-0.36	1.10	.	.	.	-0.40	0.40
25	Tyr	271	.	.	B	.	.	.	0.21	0.67	.	*	.	-0.40	0.82
	Gly	272	.	.	B	.	.	T	-0.03	0.74	.	.	.	-0.20	0.80
	Met	273	.	.	B	.	.	T	0.47	0.84	.	.	.	-0.20	0.93
	Asp	274	.	.	B	.	.	T	0.17	0.54	.	.	.	-0.20	0.86
	Tyr	275	A	T	0.91	0.17	.	.	.	0.25	1.16
30	Ala	276	A	1.16	-0.26	.	.	.	0.65	2.34
	Thr	277	A	0.91	-0.87	.	*	F	1.10	2.34
	Ser	278	A	T	1.62	-0.37	*	.	F	1.00	1.51
	Lys	279	A	T	1.62	-1.13	.	.	F	1.30	2.93
	Asp	280	A	T	1.66	-1.63	*	*	F	1.30	3.52
35	Ala	281	A	T	1.39	-1.69	.	.	F	1.30	4.06
	Arg	282	.	.	B	.	.	.	0.84	-1.43	.	.	F	1.10	1.51
	Glu	283	.	.	B	B	.	.	0.80	-0.79	*	.	F	0.75	0.67
	Pro	284	.	.	B	B	.	.	0.17	-0.36	*	.	F	0.45	0.66
	Val	285	.	.	B	B	.	.	0.28	-0.36	*	*	.	0.30	0.34
40	Val	286	.	.	B	B	.	.	0.62	-0.36	*	.	.	0.30	0.38
	Gly	287	.	.	B	.	.	T	-0.38	0.40	*	.	.	-0.20	0.39
	Ala	288	.	.	B	.	.	T	-0.38	0.66	.	.	.	-0.20	0.37
	Arg	289	.	.	B	.	.	T	-0.48	0.41	*	.	.	-0.20	0.85
	Tyr	290	.	.	B	.	.	T	-0.43	0.26	*	*	.	0.25	1.25
45	Ile	291	.	A	B	B	.	.	0.47	0.51	*	*	.	-0.45	1.02
	Gln	292	.	A	B	B	.	.	0.81	0.01	*	.	.	-0.15	1.04
	Thr	293	.	A	B	B	.	.	1.37	0.01	*	*	F	0.00	1.11
	Leu	294	.	A	B	B	.	.	1.37	-0.24	*	.	F	0.90	2.15
	Lys	295	.	A	.	B	.	T	1.40	-0.93	.	*	F	1.90	2.43
50	Asp	296	.	A	.	.	.	T	2.40	-0.90	.	*	F	2.20	2.60
	His	297	.	A	1.80	-1.39	.	*	F	2.30	6.18
	Arg	298	T	1.26	-1.46	.	*	F	3.00	3.06
	Pro	299	.	.	B	.	.	T	1.78	-0.81	.	*	F	2.50	1.36
	Arg	300	.	.	B	.	.	T	1.73	0.10	.	*	.	1.15	1.05
55	Met	301	.	.	B	.	.	T	1.43	-0.40	.	*	.	1.30	0.90
	Val	302	.	.	B	.	.	.	1.47	-0.01	.	*	.	0.80	0.78
	Trp	303	.	.	B	.	.	T	0.97	-0.04	.	*	.	0.70	0.69
	Asp	304	T	0.88	0.39	.	*	F	0.45	0.89
	Ser	305	T	0.77	0.16	.	*	F	0.60	1.60
	Gln	306	T	1.33	-0.49	.	.	F	1.20	2.64
60	Xxx	307	.	A	1.49	-0.90	.	.	F	1.10	2.15
	Ser	308	A	A	1.08	-0.11	.	.	F	0.60	1.39
	Glu	309	A	A	1.08	0.29	.	.	F	-0.15	0.69
	His	310	A	A	1.13	-0.11	.	.	.	0.30	0.94

	Phe	311	A	A	1.18	0.21	.	.	.	-0.15	1.10
	Phe	312	A	A	1.61	-0.17	.	.	.	0.45	1.27
	Glu	313	A	A	1.61	-0.17	.	.	.	0.79	1.87
5	Tyr	314	A	A	1.72	-0.29	.	.	.	1.13	2.89
	Lys	315	A	A	1.46	-1.07	.	.	F	1.92	6.53
	Lys	316	.	A	.	.	T	.	1.81	-1.47	.	.	F	2.66	5.05
	Ser	317	T	T	2.62	-1.04	*	.	F	3.40	3.19
	Arg	318	T	T	2.59	-1.80	*	.	F	3.06	3.13
	Ser	319	T	T	1.98	-1.30	*	.	F	2.72	2.13
10	Gly	320	T	T	1.08	-0.66	*	.	F	2.38	1.18
	Arg	321	.	.	B	B	.	.	0.33	-0.40	.	.	F	0.79	0.45
	His	322	.	.	B	B	.	.	0.39	0.39	*	.	.	-0.30	0.29
	Val	323	.	.	B	B	.	.	0.07	0.76	*	.	.	-0.60	0.46
	Val	324	.	.	B	B	.	.	0.06	0.76	.	.	.	-0.60	0.36
15	Phe	325	.	.	B	B	.	.	-0.41	1.24	.	*	.	-0.60	0.38
	Tyr	326	.	.	B	B	.	.	-0.48	1.43	.	*	.	-0.60	0.42
	Pro	327	.	.	B	B	.	.	-0.74	0.79	.	.	F	-0.30	1.14
	Thr	328	.	A	.	.	T	.	-0.70	0.53	.	.	F	0.10	1.77
	Leu	329	A	A	0.16	0.43	*	.	F	-0.45	0.93
20	Lys	330	A	A	0.00	0.07	.	*	F	0.00	1.04
	Ser	331	A	A	0.36	0.29	.	*	F	-0.15	0.54
	Leu	332	A	A	-0.24	-0.20	.	*	.	0.45	1.28
	Gln	333	.	A	B	.	.	.	0.07	-0.20	.	*	.	0.30	0.53
	Val	334	.	A	B	.	.	.	0.07	-0.20	.	*	.	0.30	0.68
25	Arg	335	A	A	-0.57	0.10	.	*	.	-0.30	0.68
	Leu	336	A	A	-0.16	-0.09	.	*	.	0.30	0.40
	Glu	337	A	A	0.66	-0.49	*	*	.	0.45	1.05
	Leu	338	A	A	-0.16	-1.13	.	*	.	0.60	0.93
	Ala	339	A	A	0.36	-0.44	.	*	.	0.30	0.93
30	Arg	340	A	A	-0.61	-0.70	.	*	.	0.60	0.53
	Glu	341	A	A	.	B	.	.	-0.14	-0.06	*	.	.	0.30	0.48
	Leu	342	A	A	.	B	.	.	-1.00	-0.31	*	.	.	0.30	0.47
	Gly	343	A	A	.	B	.	.	-0.49	-0.17	*	*	.	0.30	0.18
35	Val	344	.	.	B	B	.	.	-0.79	0.21	*	.	.	-0.30	0.14
	Gly	345	.	.	B	B	.	.	-1.19	0.90	*	.	.	-0.60	0.12
	Val	346	.	.	B	B	.	.	-1.19	1.13	.	*	.	-0.60	0.12
	Ser	347	.	.	B	B	.	.	-1.19	0.70	.	.	.	-0.60	0.29
	Ile	348	.	.	B	B	.	.	-1.19	0.74	.	.	.	-0.60	0.24
	Trp	349	.	.	B	B	.	.	-0.33	0.74	.	.	.	-0.60	0.32
40	Glu	350	.	.	B	B	.	.	-0.33	0.50	*	.	.	-0.51	0.41
	Leu	351	.	.	B	.	.	.	-0.29	0.54	.	.	.	-0.22	0.58
	Gly	352	T	T	0.01	0.54	*	.	F	0.62	0.46
	Gln	353	T	T	0.66	-0.37	*	.	F	1.61	0.44
	Gly	354	T	0.24	0.39	*	.	F	0.90	0.84
45	Leu	355	T	0.00	0.49	*	.	.	0.36	0.73
	Asp	356	.	.	B	B	.	.	0.81	0.81	*	.	.	-0.33	0.66
	Tyr	357	.	.	B	B	.	.	0.34	0.41	*	.	.	-0.27	1.12
	Phe	358	.	A	B	B	.	.	-0.47	0.67	*	.	.	-0.36	1.12
	Tyr	359	.	A	B	B	.	.	-0.51	0.67	*	.	.	-0.60	0.55
50	Asp	360	.	A	B	B	.	.	-0.09	1.10	*	.	.	-0.60	0.45
	Leu	361	.	A	B	B	.	.	-0.48	0.77	*	.	.	-0.60	0.67
	Leu	362	A	A	.	B	.	.	-0.62	0.41	.	.	.	-0.60	0.54

Table 4

(Gene No: 113 / Clone ID: HCE3Q10)

5	Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
	Met 1	.	.	B	-0.39	0.26	.	.	.	-0.10	0.57
	Gly 2	A	-0.59	0.33	.	.	.	-0.10	0.45
	Ala 3	A	A	-0.50	0.40	.	.	.	-0.30	0.36
10	Pro 4	A	A	-0.92	0.36	.	.	.	-0.30	0.48
	Ala 5	A	A	-1.34	0.43	.	.	.	-0.60	0.40
	Ala 6	A	A	-1.56	0.69	.	.	.	-0.60	0.33
	Ser 7	A	A	-2.02	0.87	.	.	.	-0.60	0.18
	Leu 8	A	A	-2.24	1.13	.	.	.	-0.60	0.14
15	Leu 9	A	A	-2.84	1.31	.	.	.	-0.60	0.12
	Leu 10	A	A	-3.07	1.50	.	.	.	-0.60	0.07
	Leu 11	A	A	-3.18	1.80	.	.	.	-0.60	0.07
	Leu 12	A	A	-3.47	1.90	.	.	.	-0.60	0.08
	Leu 13	A	A	-3.32	1.71	.	.	.	-0.60	0.09
20	Leu 14	A	A	-3.18	1.60	.	.	.	-0.60	0.06
	Phe 15	.	A	B	-2.66	1.49	.	.	.	-0.60	0.04
	Ala 16	.	A	B	-2.43	1.71	.	.	.	-0.60	0.05
	Cys 17	.	A	B	-1.83	1.53	.	.	.	-0.60	0.06
	Cys 18	.	A	B	-1.37	1.27	.	.	.	-0.60	0.11
25	Trp 19	.	A	B	-0.90	0.91	.	.	.	-0.60	0.11
	Ala 20	T	C	-0.79	0.84	.	.	.	0.00	0.20
	Pro 21	T	T	.	-0.20	0.77	*	.	F	0.35	0.37
	Gly 22	T	T	.	-0.34	0.60	.	.	F	0.35	0.57
	Gly 23	T	T	.	0.02	0.37	*	.	F	0.65	0.47
30	Ala 24	C	0.31	0.26	*	.	F	0.25	0.40
	Asn 25	C	0.90	0.23	*	*	F	0.25	0.71
	Leu 26	.	.	B	0.77	-0.20	*	*	F	0.80	1.19
	Ser 27	.	.	B	.	.	T	.	0.87	-0.20	.	*	F	1.00	1.17
	Gln 28	T	T	.	0.92	0.06	.	*	F	0.80	1.14
35	Asp 29	T	T	.	1.51	0.57	.	*	F	0.50	1.45
	Gly 30	T	C	1.51	0.29	.	*	F	0.60	1.87
	Tyr 31	.	A	.	.	T	.	.	2.32	-0.10	.	.	.	0.85	1.87
	Trp 32	.	A	B	2.62	-0.10	.	.	F	0.60	1.94
	Gln 33	.	A	B	1.81	-0.10	.	.	F	0.60	3.28
40	Glu 34	.	A	B	1.81	0.16	.	*	F	0.00	1.72
	Gln 35	A	A	1.34	-0.60	.	.	F	0.90	2.84
	Asp 36	A	A	1.24	-0.83	.	.	F	0.90	1.35
	Leu 37	A	A	1.22	-0.80	.	.	F	0.75	0.77
	Glu 38	A	A	0.41	-0.31	.	.	F	0.45	0.64
45	Leu 39	A	A	-0.18	-0.03	.	*	.	0.30	0.32
	Gly 40	A	A	-0.39	0.47	.	.	.	-0.60	0.39
	Thr 41	A	A	-1.20	0.21	.	*	.	-0.30	0.35
	Leu 42	A	A	-0.39	0.90	.	.	.	-0.60	0.35
	Ala 43	A	A	-0.39	0.21	.	.	.	-0.30	0.59
50	Pro 44	A	A	-0.17	-0.21	*	.	.	0.30	0.70
	Leu 45	A	A	-0.71	-0.20	*	.	.	0.30	0.86
	Asp 46	A	A	-0.70	-0.20	*	.	.	0.30	0.60
	Glu 47	A	A	-0.19	-0.31	*	.	.	0.30	0.52
	Ala 48	A	.	.	B	.	.	.	0.09	-0.36	*	*	.	0.30	0.84
55	Ile 49	.	.	B	B	.	.	.	-0.56	-0.56	*	.	F	0.75	0.73
	Ser 50	.	.	B	B	.	.	.	-0.03	0.09	*	.	F	-0.15	0.31
	Ser 51	.	.	B	B	.	.	.	-0.33	1.00	.	.	F	-0.45	0.33
	Thr 52	.	.	B	B	.	.	.	-0.63	0.89	.	.	F	-0.45	0.62
	Val 53	.	.	.	B	T	.	.	-0.26	0.59	*	.	F	-0.05	0.62
60	Trp 54	.	.	.	B	T	.	.	0.63	0.63	*	.	F	-0.05	0.72
	Ser 55	.	.	.	B	.	.	C	0.33	0.24	*	.	F	0.05	0.83
	Ser 56	T	C	-0.18	0.37	*	.	F	0.60	1.11

5	Pro	57	T	C	-0.46	0.41	*	.	F	0.15	0.87
	Asp	58	T	T	.	0.10	0.00	*	.	F	1.25	0.65
	Met	59	.	.	B	.	.	T	.	0.39	0.00	.	.	.	0.70	0.65
	Leu	60	.	.	B	0.69	0.01	.	.	.	0.24	0.73
	Ala	61	.	.	B	0.69	-0.41	.	.	.	1.18	0.73
	Ser	62	.	.	B	.	.	T	.	0.90	-0.03	.	.	F	1.87	0.99
	Gln	63	T	T	.	0.69	-0.24	.	.	F	2.76	2.08
	Asp	64	T	T	.	1.00	-0.50	.	.	F	3.40	3.19
10	Ser	65	T	C	1.50	-0.09	*	.	F	2.56	2.50
	Gln	66	C	1.79	0.01	.	.	F	1.66	2.08
	Pro	67	T	.	.	2.09	0.00	.	.	F	2.36	1.67
	Trp	68	C	2.09	0.00	.	.	F	2.06	2.08
	Thr	69	T	C	1.78	-0.39	.	.	F	2.16	2.08
	Ser	70	T	C	1.22	-0.30	.	.	F	2.40	1.95
15	Asp	71	.	.	B	.	.	T	.	0.37	-0.09	.	.	F	1.96	1.37
	Glu	72	.	.	B	.	.	T	.	-0.01	-0.36	.	.	F	1.57	0.71
	Thr	73	.	.	B	-0.07	-0.34	.	.	F	1.13	0.53
	Val	74	.	.	B	-0.10	-0.30	.	.	.	0.74	0.32
20	Val	75	.	.	B	.	.	T	.	-0.11	0.13	.	.	.	0.10	0.18
	Ala	76	A	T	.	-0.97	0.61	.	.	.	-0.20	0.18
	Gly	77	A	T	.	-1.82	0.77	.	.	F	-0.05	0.18
	Gly	78	A	T	.	-2.32	0.77	*	*	F	-0.05	0.18
	Thr	79	A	.	.	B	.	.	.	-1.42	0.81	*	*	F	-0.45	0.15
25	Val	80	A	.	.	B	B	.	.	-1.23	0.31	.	*	.	-0.30	0.30
	Val	81	.	.	B	B	.	.	.	-0.64	0.46	.	*	.	-0.60	0.16
	Leu	82	.	.	B	B	.	.	.	-1.16	0.43	*	*	.	-0.60	0.19
	Lys	83	.	.	B	B	.	.	.	-0.77	0.59	*	*	.	-0.60	0.19
	Cys	84	.	.	B	B	.	.	.	-0.46	-0.06	.	*	.	0.30	0.52
30	Gln	85	A	.	.	B	B	.	.	0.37	-0.70	.	*	.	0.75	1.05
	Val	86	A	.	.	B	B	.	.	1.22	-0.89	*	*	.	0.60	0.72
	Lys	87	.	.	B	B	.	.	.	2.03	-0.89	*	*	F	1.24	2.32
	Asp	88	A	1.69	-1.46	.	*	F	1.78	2.24
	His	89	A	2.06	-1.47	.	*	F	2.12	4.04
35	Glu	90	A	1.24	-1.73	*	*	F	2.46	2.71
	Asp	91	T	T	.	2.10	-1.04	*	*	F	3.40	1.34
	Ser	92	T	T	.	1.77	-0.64	.	*	F	3.06	1.70
	Ser	93	T	T	.	1.47	-0.23	.	.	F	2.42	1.03
	Leu	94	T	T	.	1.50	0.16	.	*	.	1.18	0.83
40	Gln	95	T	.	.	1.29	0.56	*	*	.	0.34	0.99
	Trp	96	T	.	.	0.70	0.60	*	*	.	0.15	1.15
	Ser	97	C	1.00	0.71	*	*	F	0.10	1.41
	Asn	98	T	C	1.30	0.43	*	*	F	0.30	1.41
	Pro	99	T	C	1.80	0.43	*	*	F	0.30	2.31
45	Ala	100	T	T	.	0.99	0.00	*	.	F	1.40	2.49
	Gln	101	.	.	B	.	.	T	.	1.03	0.30	*	.	F	0.40	1.28
	Gln	102	.	.	B	B	.	.	.	0.63	0.66	*	.	F	-0.30	1.30
	Thr	103	.	.	B	B	.	.	.	0.29	1.01	*	.	F	-0.30	1.11
	Leu	104	.	.	B	B	.	.	.	0.50	0.94	*	.	.	-0.60	0.63
50	Tyr	105	.	.	B	1.13	0.54	*	.	.	-0.40	0.63
	Phe	106	.	A	B	1.24	0.14	*	.	.	-0.30	0.88
	Gly	107	A	A	0.66	-0.34	*	.	F	0.60	2.09
	Glu	108	A	A	0.16	-0.53	*	.	F	0.90	1.35
	Lys	109	A	A	1.08	-0.60	*	.	F	0.90	1.28
55	Arg	110	A	A	1.32	-1.39	*	.	F	0.90	2.54
	Ala	111	A	A	2.02	-1.81	*	.	F	0.90	2.45
	Leu	112	A	A	2.48	-1.41	*	.	F	0.90	1.97
	Arg	113	A	T	.	1.59	-1.41	*	*	F	1.30	1.97
	Asp	114	A	T	.	1.54	-0.73	*	*	F	1.30	1.37
60	Asn	115	A	T	.	0.62	-0.83	*	*	F	1.30	2.87
	Arg	116	.	.	B	.	.	T	.	0.36	-0.83	.	*	F	1.30	1.21
	Ile	117	.	.	B	B	.	.	.	0.86	-0.19	.	*	.	0.30	0.54
	Gln	118	.	.	B	B	.	.	.	0.44	0.30	.	*	.	-0.30	0.48
	Leu	119	.	.	B	B	.	.	.	0.13	0.29	.	*	.	-0.30	0.33

	Val	120	.	.	B	B	.	.	-0.08	0.77	.	*	.	-0.36	0.68
	Thr	121	.	.	B	B	.	.	-0.22	0.51	.	*	F	0.03	0.61
	Ser	122	.	.	B	.	.	.	0.67	0.61	*	.	F	0.47	1.00
5	Thr	123	T	-0.14	-0.07	*	.	F	2.16	2.33
	Pro	124	T	0.37	-0.03	.	*	F	2.40	1.33
	His	125	T	0.33	-0.13	.	*	F	2.16	1.33
	Glu	126	.	.	B	.	.	T	0.34	0.17	.	*	.	0.82	0.65
	Leu	127	.	.	B	B	.	.	-0.24	0.07	.	*	.	0.18	0.56
10	Ser	128	.	.	B	B	.	.	-0.23	0.33	*	*	.	-0.06	0.29
	Ile	129	.	.	B	B	.	.	-0.02	0.21	*	*	.	-0.30	0.22
	Ser	130	.	.	B	B	.	.	-0.84	0.61	*	*	.	-0.60	0.44
	Ile	131	.	.	B	B	.	.	-1.43	0.57	.	*	.	-0.60	0.24
	Ser	132	.	.	B	B	.	.	-1.43	0.69	.	*	.	-0.60	0.35
15	Asn	133	.	A	B	.	.	.	-1.72	0.69	.	.	.	-0.60	0.21
	Val	134	.	A	B	.	.	.	-0.83	0.80	.	.	.	-0.60	0.31
	Ala	135	.	A	B	.	.	.	-0.53	0.11	.	.	.	-0.30	0.38
	Leu	136	A	A	0.01	-0.27	.	.	.	0.30	0.41
	Ala	137	A	A	0.31	-0.24	.	.	.	0.30	0.55
20	Asp	138	A	A	0.07	-0.89	.	.	F	0.75	0.95
	Glu	139	A	A	0.61	-0.63	.	.	F	0.90	1.80
	Gly	140	A	0.53	-0.83	*	.	F	1.10	2.57
	Glu	141	A	1.04	-0.76	*	*	F	0.95	0.82
	Tyr	142	A	T	0.74	-0.37	*	.	.	0.70	0.64
25	Thr	143	A	T	0.04	0.31	*	.	.	0.10	0.45
	Cys	144	.	.	B	.	.	T	-0.27	0.67	.	*	.	-0.20	0.23
	Ser	145	.	.	B	.	.	T	-0.52	1.16	*	.	.	-0.20	0.21
	Ile	146	.	.	B	B	.	.	-0.73	1.01	.	.	.	-0.60	0.14
	Phe	147	.	.	B	B	.	.	-1.34	0.96	*	*	.	-0.60	0.41
30	Thr	148	.	.	B	B	.	.	-0.92	1.03	*	*	.	-0.60	0.23
	Met	149	.	.	B	B	.	.	-0.57	0.64	*	*	.	-0.60	0.64
	Pro	150	.	.	B	B	.	.	-0.86	0.44	*	.	.	-0.45	1.06
	Val	151	A	.	.	B	.	.	0.08	0.16	*	.	.	-0.30	0.74
	Arg	152	A	.	.	B	.	.	0.48	-0.33	*	*	F	0.60	1.50
35	Thr	153	A	.	.	B	.	.	-0.02	-0.56	*	*	F	0.90	1.30
	Ala	154	A	.	.	B	.	.	-0.28	-0.30	*	*	F	0.60	1.45
	Lys	155	A	.	.	B	.	.	-0.38	-0.30	*	*	F	0.45	0.55
	Ser	156	.	.	B	B	.	.	-0.38	0.19	*	.	F	-0.15	0.55
	Leu	157	.	.	B	B	.	.	-1.30	0.34	*	.	.	-0.30	0.40
40	Val	158	.	.	B	B	.	.	-1.33	0.53	*	.	.	-0.60	0.17
	Thr	159	.	.	B	B	.	.	-1.63	0.96	*	.	.	-0.60	0.12
	Val	160	.	.	B	B	.	.	-1.89	1.26	*	.	.	-0.60	0.10
	Leu	161	.	.	B	B	.	.	-1.59	1.00	*	.	.	-0.60	0.22
	Gly	162	.	.	B	B	.	.	-0.73	0.76	*	.	.	-0.60	0.26
45	Ile	163	.	.	B	B	.	.	-0.09	0.27	*	.	F	-0.15	0.70
	Pro	164	.	.	.	B	.	.	-0.67	0.06	*	.	F	0.20	1.32
	Gln	165	.	.	B	.	.	.	-0.70	0.06	*	.	F	0.05	0.93
	Lys	166	.	.	B	B	.	.	-0.20	0.31	.	.	F	-0.15	0.93
	Pro	167	.	.	B	B	.	.	-0.20	0.11	.	.	F	-0.15	0.87
50	Ile	168	.	.	B	B	.	.	0.44	0.11	*	.	.	-0.30	0.50
	Ile	169	.	.	B	B	.	.	0.70	0.47	*	.	.	-0.60	0.39
	Thr	170	.	.	B	B	.	.	0.40	0.47	*	.	.	-0.60	0.50
	Gly	171	.	.	B	.	.	.	0.06	0.43	*	.	F	0.05	0.96
	Tyr	172	.	.	B	.	.	T	-0.54	0.13	*	*	F	1.00	1.84
	Lys	173	T	0.46	0.13	*	*	F	1.50	1.05
55	Ser	174	T	1.34	-0.36	*	*	F	2.40	2.08
	Ser	175	T	1.70	-0.79	*	*	F	3.00	2.30
	Leu	176	.	A	B	.	.	.	2.04	-1.54	*	*	F	2.10	2.30
	Arg	177	A	A	1.98	-1.54	*	*	F	1.80	2.87
60	Glu	178	A	A	1.34	-1.44	*	*	F	1.50	3.09
	Lys	179	A	A	1.33	-1.33	.	*	F	1.20	3.79
	Asp	180	A	A	0.82	-1.53	.	*	F	0.90	2.79
	Thr	181	A	A	1.63	-0.84	.	*	F	0.90	1.33
	Ala	182	A	A	0.86	-0.44	.	*	F	0.60	1.07

5	Thr	183	.	A	B	.	.	.	0.86	0.13	.	*	.	-0.30	0.34	
	Leu	184	.	A	B	.	.	.	0.51	0.53	.	*	.	-0.60	0.41	
	Asn	185	.	A	B	.	.	.	0.21	0.43	.	*	.	-0.60	0.55	
	Cys	186	.	.	B	.	.	.	0.18	0.31	.	*	F	0.39	0.51	
	Gln	187	T	.	0.47	0.26	.	*	F	1.13	0.61	
10	Ser	188	T	T	0.82	-0.04	.	*	F	2.27	0.51	
	Ser	189	T	T	1.42	-0.44	*	*	F	2.76	1.89	
	Gly	190	T	T	0.83	-0.59	*	.	F	3.40	1.69	
	Ser	191	T	C	0.91	-0.49	*	*	F	2.56	1.27
	Lys	192	.	A	C	1.02	-0.37	*	*	F	1.67	0.96
15	Pro	193	.	A	C	0.51	-0.76	*	*	F	1.78	1.90
	Ala	194	.	A	B	0.50	-0.50	*	*	F	1.24	1.17
	Ala	195	.	A	B	B	.	.	.	0.56	-0.40	*	*	.	0.30	0.84
	Arg	196	.	A	B	B	.	.	.	0.97	0.51	*	*	.	-0.60	0.57
	Leu	197	.	A	B	B	.	.	.	0.97	0.09	*	*	.	0.19	1.11
20	Thr	198	A	A	.	B	.	.	.	0.83	-0.41	*	*	.	1.13	2.20
	Trp	199	A	A	.	B	.	.	.	1.42	-0.49	*	*	.	1.47	1.11
	Arg	200	T	C	2.01	-0.49	*	*	F	2.56	2.25
	Lys	201	T	T	.	1.90	-0.77	*	*	F	3.40	2.70
	Gly	202	T	T	.	1.90	-1.26	*	*	F	3.06	4.45
25	Asp	203	T	C	2.18	-1.49	*	*	F	2.52	1.87
	Gln	204	.	A	C	2.12	-0.99	*	*	F	1.78	1.28
	Glu	205	.	A	C	2.01	-0.56	*	*	F	1.44	1.28
	Leu	206	.	A	C	1.76	-0.99	*	*	F	1.10	1.32
	His	207	.	A	.	.	T	.	.	1.79	-0.56	*	*	F	1.64	1.18
30	Gly	208	.	A	C	1.90	-0.47	*	*	F	1.33	0.98
	Glu	209	T	C	1.01	-0.47	*	*	F	2.22	2.34
	Pro	210	T	C	1.01	-0.47	*	*	F	2.56	1.20
	Thr	211	T	T	.	1.82	-0.57	*	*	F	3.40	2.11
	Arg	212	.	.	B	.	.	T	.	1.86	-1.00	*	*	F	2.66	2.11
35	Ile	213	.	.	B	1.99	-1.00	*	*	F	2.46	2.28
	Gln	214	.	.	B	1.99	-1.00	*	*	F	2.46	2.44
	Glu	215	.	.	B	1.86	-1.09	*	*	F	2.46	2.00
	Asp	216	T	C	2.21	-0.66	*	*	F	2.86	2.83
	Pro	217	T	T	.	1.79	-1.34	.	*	F	3.40	3.26
40	Asn	218	T	T	.	1.98	-1.26	.	*	F	3.06	2.72
	Gly	219	T	T	.	1.67	-0.47	.	*	F	2.42	1.41
	Lys	220	.	.	.	B	T	.	.	0.81	0.01	.	.	F	1.08	1.32
	Thr	221	.	.	B	B	.	.	.	0.51	0.23	.	.	F	0.19	0.61
	Phe	222	.	.	B	B	.	.	.	0.42	0.21	.	.	F	-0.15	0.82
45	Thr	223	.	.	B	B	.	.	.	0.12	0.17	.	*	.	-0.30	0.55
	Val	224	.	.	B	.	.	T	.	-0.39	0.56	.	.	F	-0.05	0.51
	Ser	225	.	.	B	.	.	T	.	-0.74	0.71	.	*	F	-0.05	0.44
	Ser	226	T	C	-1.13	0.41	.	*	F	0.15	0.44
	Ser	227	T	C	-0.43	0.71	.	*	F	0.15	0.51
50	Val	228	.	.	B	B	.	.	.	-0.98	0.47	.	*	F	-0.45	0.66
	Thr	229	.	.	B	B	.	.	.	-0.43	0.73	*	*	.	-0.60	0.37
	Phe	230	.	.	B	B	.	.	.	-0.02	0.83	*	*	.	-0.60	0.39
	Gln	231	.	.	B	B	.	.	.	0.28	0.44	*	*	.	-0.45	1.04
	Val	232	.	.	B	B	.	.	.	0.58	-0.20	*	*	.	0.79	1.25
55	Thr	233	.	.	B	B	.	.	.	1.43	-0.69	*	*	F	1.58	2.41
	Arg	234	.	.	B	B	.	.	.	1.40	-1.47	*	.	F	1.92	2.32
	Glu	235	.	.	.	B	T	.	.	1.51	-1.44	*	.	F	2.66	3.10
	Asp	236	T	T	.	1.21	-1.59	.	.	F	3.40	2.17
	Asp	237	T	T	.	1.18	-1.69	*	.	F	3.06	1.48
60	Gly	238	T	T	.	0.63	-1.00	.	.	F	2.57	0.60
	Ala	239	A	T	.	-0.14	-0.36	.	.	.	1.38	0.27
	Ser	240	.	.	B	B	.	.	.	-0.44	0.21	*	.	.	0.04	0.09
	Ile	241	.	.	B	B	.	.	.	-1.30	0.60	*	.	.	-0.60	0.12
	Val	242	.	.	B	B	.	.	.	-1.30	0.81	*	.	.	-0.60	0.09
	Cys	243	.	.	B	B	.	.	.	-0.99	0.71	*	*	.	-0.60	0.10
	Ser	244	.	.	B	B	.	.	.	-0.40	0.83	.	*	.	-0.60	0.20
	Val	245	.	.	B	B	.	.	.	-0.40	0.14	.	.	.	-0.30	0.46

5	Asn	246	A	.	.	B	.	.	.	-0.32	-0.11	*	.	.	0.45	1.16
	His	247	A	A	0.58	0.00	*	.	.	0.30	0.71
	Glu	248	A	A	0.90	-0.39	*	.	F	0.60	1.92
	Ser	249	A	A	0.61	-0.60	*	.	F	0.90	1.18
	Leu	250	A	A	1.47	-0.50	*	*	F	0.75	0.88
	Lys	251	A	A	1.58	-1.00	*	*	F	0.75	0.85
	Gly	252	A	T	.	1.31	-1.00	*	*	F	1.60	1.24
	Ala	253	A	T	.	1.00	-1.00	*	*	F	1.90	2.01
10	Asp	254	A	T	.	1.00	-1.20	*	*	F	2.20	1.45
	Arg	255	A	T	.	1.81	-0.81	*	*	F	2.50	1.96
	Ser	256	T	C	1.88	-0.84	*	*	F	3.00	3.37
	Thr	257	T	C	1.33	-1.34	*	*	F	2.70	3.95
	Ser	258	T	C	1.92	-0.66	*	*	F	2.40	1.41
15	Gln	259	.	.	B	.	.	T	.	1.07	-0.66	*	*	F	1.90	1.83
	Arg	260	.	.	B	B	.	.	.	0.14	-0.40	*	*	F	0.75	0.94
	Ile	261	.	.	B	B	.	.	.	0.20	-0.20	*	*	F	0.45	0.58
	Glu	262	.	.	B	B	.	.	.	0.20	0.17	.	*	.	-0.30	0.52
	Val	263	.	.	B	B	.	.	.	0.29	0.26	.	*	.	-0.30	0.39
20	Leu	264	.	.	B	B	.	.	.	-0.02	0.69	*	*	.	-0.60	0.85
	Tyr	265	.	.	B	B	.	.	.	-0.72	0.49	.	*	.	-0.60	0.71
	Thr	266	.	.	B	.	.	T	.	-0.43	0.99	*	*	.	-0.20	0.96
	Pro	267	T	C	-1.32	0.96	*	*	F	0.30	1.16
	Thr	268	.	.	B	.	.	T	.	-0.36	0.96	*	*	.	-0.20	0.52
25	Ala	269	.	.	B	.	.	T	.	0.24	0.20	.	*	.	0.10	0.70
	Met	270	.	.	B	0.49	0.14	.	*	.	-0.10	0.70
	Ile	271	.	.	B	0.59	-0.29	.	*	.	0.50	0.81
	Arg	272	.	.	B	.	.	T	.	0.59	-0.34	.	*	.	0.85	1.24
	Pro	273	T	T	.	0.87	-0.41	.	*	F	1.40	1.94
30	Asp	274	T	C	1.24	-0.53	*	*	F	1.50	3.77
	Pro	275	T	C	1.96	-0.79	*	*	F	1.84	2.98
	Pro	276	C	2.84	-0.79	*	*	F	1.98	3.77
	His	277	T	C	2.39	-1.21	*	*	F	2.52	3.91
	Pro	278	T	C	2.60	-0.79	*	*	F	2.86	2.50
35	Arg	279	T	T	.	2.64	-0.81	*	*	F	3.40	2.80
	Glu	280	A	T	.	2.04	-1.24	*	.	F	2.66	4.12
	Gly	281	A	A	1.44	-1.06	*	*	F	1.92	2.20
	Gln	282	A	A	0.67	-0.80	*	*	F	1.43	0.93
	Lys	283	A	A	0.84	-0.11	*	*	F	0.79	0.44
40	Leu	284	A	A	0.07	0.39	*	*	F	-0.15	0.61
	Leu	285	.	A	B	0.07	0.53	*	*	.	-0.60	0.19
	Leu	286	.	A	B	0.07	0.13	*	*	.	-0.30	0.16
	His	287	.	A	B	0.18	0.56	*	*	.	-0.26	0.19
	Cys	288	.	A	B	-0.21	-0.13	*	*	.	0.98	0.46
45	Glu	289	.	A	.	.	T	.	.	0.60	-0.39	.	*	F	1.87	0.56
	Gly	290	T	T	.	1.20	-0.67	.	*	F	2.91	0.66
	Arg	291	T	T	.	1.16	-0.74	.	*	F	3.40	1.89
	Gly	292	T	T	.	0.98	-0.67	.	*	F	2.91	0.81
	Asn	293	T	C	1.64	-0.24	.	*	F	2.22	1.27
50	Pro	294	C	1.64	-0.27	.	*	F	1.68	1.12
	Val	295	C	1.74	0.13	*	*	F	0.74	1.96
	Pro	296	.	.	B	0.82	0.46	*	*	F	-0.10	1.91
	Gln	297	.	A	B	0.88	0.74	.	.	F	-0.30	1.02
	Gln	298	.	A	B	0.88	1.23	.	.	F	-0.30	1.44
55	Tyr	299	.	A	B	1.13	0.59	.	.	.	-0.45	1.62
	Leu	300	.	A	B	1.99	0.16	.	.	.	-0.15	1.87
	Trp	301	.	A	B	1.86	-0.24	.	.	.	0.45	1.87
	Glu	302	.	A	B	1.56	-0.21	.	.	F	0.60	1.18
	Lys	303	.	A	.	.	T	.	.	0.70	-0.59	.	.	F	1.30	1.92
60	Glu	304	.	A	.	.	T	.	.	0.73	-0.63	.	.	F	1.30	1.35
	Gly	305	.	A	.	.	T	.	.	1.33	-1.11	.	.	F	1.30	1.21
	Ser	306	C	0.81	-0.69	.	.	F	1.15	0.93
	Val	307	C	0.86	0.00	.	.	F	0.85	0.44
	Pro	308	T	C	0.21	0.00	.	.	F	1.05	0.90

5	Pro	309	A	T	C	-0.10	0.19	.	.	F	0.45	0.66
	Leu	310	A	T	.	0.24	0.29	.	.	F	0.40	1.29
	Lys	311	A	T	.	0.54	0.04	.	.	F	0.40	1.45
	Met	312	A	A	1.10	-0.39	*	.	F	0.60	1.62
	Thr	313	A	A	0.72	-0.43	.	*	F	0.60	2.63
10	Gln	314	A	A	0.12	-0.61	.	*	F	0.90	1.33
	Glu	315	A	A	0.04	0.07	*	*	F	0.00	1.11
	Ser	316	A	A	.	B	.	.	.	-0.70	0.14	*	.	F	-0.15	0.54
	Ala	317	A	A	.	B	.	.	.	-0.31	0.44	.	.	.	-0.60	0.27
	Leu	318	A	A	.	B	.	.	.	-0.70	0.47	.	.	.	-0.60	0.24
15	Ile	319	.	A	B	B	.	.	.	-1.51	1.26	.	.	.	-0.60	0.16
	Phe	320	.	A	B	B	.	.	.	-1.51	1.56	*	.	.	-0.60	0.13
	Pro	321	.	A	B	-1.17	1.46	*	.	.	-0.60	0.25
	Phe	322	.	.	B	-0.88	0.77	*	.	.	-0.40	0.70
	Leu	323	.	.	B	-0.07	0.47	*	.	.	0.09	1.09
20	Asn	324	T	.	.	0.52	-0.31	*	.	F	1.88	1.18
	Lys	325	T	.	.	0.88	-0.36	.	.	F	2.22	1.82
	Ser	326	T	.	.	0.78	-0.71	*	.	F	2.86	2.19
	Asp	327	T	T	.	1.23	-0.91	.	.	F	3.40	1.96
	Ser	328	T	T	.	1.70	-0.56	.	.	F	3.06	1.54
25	Gly	329	T	T	.	1.03	-0.13	.	.	F	2.42	1.14
	Thr	330	T	T	.	0.68	0.06	.	.	F	1.33	0.36
	Tyr	331	.	.	B	B	.	.	.	0.39	0.54	.	.	F	-0.11	0.39
	Gly	332	.	.	B	B	.	.	.	0.08	0.66	.	.	.	-0.60	0.40
	Cys	333	.	.	B	B	.	.	.	0.08	0.71	.	.	.	-0.60	0.40
30	Thr	334	.	.	B	B	.	.	.	0.42	0.61	.	.	.	-0.60	0.34
	Ala	335	.	.	B	B	.	.	.	0.13	0.26	.	.	F	-0.15	0.56
	Thr	336	.	.	B	B	.	.	.	0.03	0.44	.	.	F	-0.30	1.03
	Ser	337	.	.	B	B	.	.	.	0.08	0.30	.	.	F	-0.06	0.71
	Asn	338	.	.	B	.	T	T	.	0.50	0.20	.	.	F	0.83	0.94
35	Met	339	T	T	.	0.86	0.46	.	.	F	0.77	1.02
	Gly	340	T	T	.	0.86	-0.03	.	.	F	1.76	1.52
	Ser	341	T	C	0.92	0.09	.	.	F	0.90	0.95
	Tyr	342	.	.	B	B	.	.	.	0.98	0.44	.	.	.	-0.09	1.51
	Lys	343	.	.	B	B	.	.	.	0.67	0.59	.	*	.	-0.18	2.39
40	Ala	344	.	.	B	B	.	.	.	0.46	0.64	.	*	.	-0.27	2.57
	Tyr	345	.	.	B	B	.	.	.	0.80	0.94	.	*	.	-0.36	1.35
	Tyr	346	.	.	B	B	.	.	.	0.24	0.59	.	*	.	-0.45	1.09
	Thr	347	.	.	B	B	.	.	.	0.49	1.23	.	*	.	-0.60	0.80
	Leu	348	.	.	B	B	.	.	.	0.44	1.13	.	*	.	-0.36	0.82
45	Asn	349	.	.	B	B	.	.	.	0.82	0.37	.	*	.	0.18	0.87
	Val	350	.	.	B	B	.	.	.	0.77	0.04	.	*	.	0.42	0.94
	Asn	351	.	.	.	B	T	.	.	0.80	-0.06	.	*	F	1.96	1.52
	Asp	352	T	C	0.26	-0.31	.	*	F	2.40	1.46
	Pro	353	.	.	B	.	.	T	.	0.86	-0.07	.	*	F	1.96	1.46
50	Ser	354	T	C	0.56	-0.29	.	.	F	1.92	1.41
	Pro	355	.	.	B	.	.	T	.	1.11	-0.30	.	.	F	1.48	1.13
	Val	356	.	.	B	.	.	T	.	0.81	0.09	.	.	F	0.49	0.98
	Pro	357	.	.	B	.	.	T	.	0.51	0.04	.	.	F	0.25	0.98
	Ser	358	T	T	.	0.41	0.04	.	.	F	0.65	0.85
55	Ser	359	.	.	B	.	.	T	.	0.47	0.10	.	.	F	0.40	1.65
	Ser	360	.	.	B	.	.	T	.	0.64	0.21	.	.	F	0.40	1.67
	Ser	361	.	.	B	.	.	T	.	0.91	0.29	.	.	F	0.40	1.70
	Thr	362	.	.	B	.	.	T	.	0.23	0.40	.	.	F	0.40	1.28
	Tyr	363	.	.	B	.	.	T	.	-0.36	0.70	.	.	.	-0.20	0.67
60	His	364	.	.	B	B	.	.	.	-0.40	1.00	.	.	.	-0.60	0.35
	Ala	365	.	.	B	B	.	.	.	-0.44	1.04	*	.	.	-0.60	0.24
	Ile	366	.	.	B	B	.	.	.	-1.03	0.99	*	.	.	-0.60	0.15
	Ile	367	.	.	B	B	.	.	.	-1.58	0.91	.	.	.	-0.60	0.08
	Gly	368	.	.	B	B	.	.	.	-1.92	1.06	*	.	.	-0.60	0.06
60	Gly	369	.	.	B	B	.	.	.	-2.59	1.06	*	.	.	-0.60	0.08
	Ile	370	.	.	B	B	.	.	.	-2.89	1.16	.	.	.	-0.60	0.10
	Val	371	.	.	B	B	.	.	.	-2.86	1.16	.	.	.	-0.60	0.07

5	Ala	372	.	.	B	B	.	.	.	-2.67	1.37	.	.	.	-0.60	0.05
	Phe	373	.	.	B	B	.	.	.	-3.13	1.73	.	.	.	-0.60	0.07
	Ile	374	.	.	B	B	.	.	.	-3.60	1.73	.	.	.	-0.60	0.07
	Val	375	.	.	B	B	.	.	.	-3.52	1.77	.	.	.	-0.60	0.06
	Phe	376	A	.	.	B	.	.	.	-3.56	1.96	.	.	.	-0.60	0.06
	Leu	377	A	.	.	B	.	.	.	-3.57	1.86	.	.	.	-0.60	0.06
	Leu	378	A	.	.	B	.	.	.	-3.68	1.79	.	.	.	-0.60	0.08
	Leu	379	A	.	.	B	.	.	.	-3.68	1.83	.	.	.	-0.60	0.07
10	Ile	380	A	.	.	B	.	.	.	-3.52	1.73	.	.	.	-0.60	0.06
	Met	381	A	.	.	B	.	.	.	-3.63	1.83	.	.	.	-0.60	0.07
	Leu	382	A	.	.	B	.	.	.	-3.17	1.83	.	.	.	-0.60	0.07
	Ile	383	A	.	.	B	.	.	.	-2.39	1.57	.	.	.	-0.60	0.09
	Phe	384	A	.	.	B	.	.	.	-1.82	1.39	.	.	.	-0.60	0.13
	Leu	385	A	.	.	B	.	.	.	-1.74	1.53	.	.	.	-0.60	0.24
15	Gly	386	A	.	.	B	.	.	.	-2.03	1.53	*	*	.	-0.60	0.28
	His	387	A	.	.	B	.	.	.	-1.11	1.53	*	*	.	-0.60	0.23
	Tyr	388	A	.	.	B	.	.	.	-0.26	0.74	.	*	*	-0.60	0.55
	Leu	389	.	.	B	B	.	.	.	0.49	0.56	.	*	*	-0.32	0.75
20	Ile	390	.	.	B	B	.	.	.	0.96	0.13	*	*	.	0.41	1.11
	Arg	391	.	.	B	B	.	.	.	0.99	0.06	*	*	.	0.54	0.70
	His	392	T	T	.	0.78	-0.21	*	*	.	2.37	1.22
	Lys	393	T	T	.	0.21	-0.14	*	*	F	2.80	2.73
	Gly	394	T	C	0.71	-0.14	*	*	F	2.32	1.15
25	Thr	395	T	C	1.57	0.34	*	*	F	1.44	1.22
	Tyr	396	.	.	B	1.46	0.34	.	*	.	0.46	0.83
	Leu	397	.	A	B	0.90	0.34	*	*	.	0.13	1.45
	Thr	398	.	A	B	0.90	0.41	.	*	.	-0.45	1.02
	His	399	A	A	0.90	-0.07	*	*	.	0.79	1.30
30	Glu	400	A	A	0.91	-0.40	*	*	.	1.13	1.56
	Ala	401	A	A	1.16	-0.70	*	*	F	1.92	1.45
	Lys	402	.	A	.	.	T	.	.	1.97	-1.19	*	*	F	2.66	1.78
	Gly	403	T	T	.	1.69	-1.69	*	*	F	3.40	1.71
	Ser	404	T	C	1.51	-1.19	*	*	F	2.86	1.71
35	Asp	405	T	T	.	1.51	-1.26	*	*	F	2.72	1.32
	Asp	406	A	T	C	1.51	-1.26	*	*	F	2.18	2.23
	Ala	407	A	1.47	-1.19	*	.	F	1.44	1.68
	Pro	408	A	1.50	-1.57	.	.	F	1.10	1.68
	Asp	409	A	T	.	1.21	-1.09	*	.	F	1.30	1.46
40	Ala	410	A	T	.	0.32	-0.59	*	.	F	1.30	1.46
	Asp	411	A	T	.	-0.57	-0.40	*	.	F	0.85	0.66
	Thr	412	A	T	.	0.02	-0.14	*	.	F	0.85	0.28
	Ala	413	A	.	.	B	.	.	.	-0.36	0.26	.	*	.	-0.30	0.44
	Ile	414	.	.	B	B	.	.	.	-0.36	0.26	.	*	.	-0.30	0.27
45	Ile	415	.	.	B	B	.	.	.	-0.11	0.26	.	.	.	-0.30	0.32
	Asn	416	.	.	B	.	.	T	.	-0.46	0.20	.	.	.	0.10	0.31
	Ala	417	.	.	B	.	.	T	.	-0.14	0.13	.	.	F	0.25	0.44
	Glu	418	T	T	.	0.14	-0.16	.	.	F	1.40	1.09
	Gly	419	T	T	.	0.69	-0.46	.	.	F	1.55	0.91
50	Gly	420	T	.	.	1.23	-0.43	.	*	F	1.65	0.89
	Gln	421	T	C	1.23	-0.50	*	.	F	2.25	0.51
	Ser	422	T	C	1.82	-0.50	.	.	F	2.55	0.86
	Gly	423	T	C	1.87	-0.93	*	.	F	3.00	1.45
	Gly	424	T	C	2.26	-1.36	*	.	F	2.70	1.68
55	Asp	425	T	C	2.60	-1.76	*	.	F	2.58	2.50
	Asp	426	T	C	2.36	-2.14	*	.	F	2.46	4.38
	Lys	427	A	T	.	1.96	-1.81	.	.	F	2.14	6.94
	Lys	428	A	T	.	1.41	-1.46	.	.	F	2.02	3.60
	Glu	429	.	.	B	B	.	.	.	1.37	-0.77	.	.	F	1.80	1.51
60	Tyr	430	.	.	B	B	.	.	.	0.98	-0.34	.	.	.	1.02	0.97
	Phe	431	.	.	B	B	.	.	.	0.59	0.09	.	.	.	0.24	0.62
	Ile	432	A	.	.	B	.	.	.	0.16	0.51	.	.	.	-0.24	0.46

Table 5

(Gene No:62 / Clone ID HEMA80)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	.	.	B	0.59	-0.19	.	*	.	0.86	1.62
Arg	2	.	.	B	0.77	-0.19	.	*	.	1.07	1.25
Thr	3	T	C	0.34	-0.19	.	*	.	1.68	1.52
Pro	4	T	C	0.52	0.07	.	*	.	1.29	1.26
Gly	5	T	C	0.06	-0.11	.	*	F	2.10	1.00
Pro	6	T	C	-0.16	0.53	.	*	F	0.99	0.51
Leu	7	.	A	B	-1.08	0.73	.	*	F	0.18	0.27
Pro	8	.	A	B	-1.58	0.99	.	.	.	-0.18	0.23
Val	9	.	A	B	-2.18	1.24	.	.	.	-0.39	0.12
Leu	10	.	A	B	-2.64	1.50	.	.	.	-0.60	0.12
Leu	11	.	A	B	-3.02	1.50	.	.	.	-0.60	0.06
Leu	12	.	A	B	-2.56	1.57	.	.	.	-0.60	0.09
Leu	13	.	A	B	-2.93	1.36	.	.	.	-0.60	0.11
Leu	14	.	A	B	-2.29	1.17	.	.	.	-0.60	0.13
Ala	15	.	A	B	-2.07	0.91	.	.	.	-0.60	0.24
Gly	16	.	A	B	-1.84	0.73	.	.	.	-0.60	0.30
Ala	17	.	.	B	-0.92	0.54	.	.	.	-0.40	0.37
Pro	18	.	.	B	-0.32	-0.14	.	.	.	0.74	0.71
Ala	19	T	.	.	0.18	-0.21	.	.	.	1.53	1.11
Ala	20	.	.	B	0.56	-0.16	.	.	.	1.37	1.58
Arg	21	.	.	B	0.69	-0.23	.	.	F	1.76	1.58
Pro	22	T	.	.	0.97	-0.23	.	.	F	2.40	2.42
Thr	23	C	0.51	-0.24	.	.	F	1.96	3.46
Pro	24	T	C	0.86	-0.17	.	.	F	1.77	0.95
Pro	25	T	T	.	1.14	0.59	.	*	F	0.83	0.96
Thr	26	T	T	.	1.14	0.54	.	*	F	0.59	0.89
Cys	27	.	.	B	.	.	T	.	0.76	0.06	.	*	.	0.25	1.13
Tyr	28	.	.	B	1.18	0.24	.	*	.	-0.10	0.72
Ser	29	.	A	B	0.80	-0.19	.	*	.	0.30	0.98
Arg	30	.	A	B	0.20	-0.17	.	*	.	0.45	1.85
Met	31	.	A	B	0.21	-0.06	.	*	.	0.30	0.97
Arg	32	.	A	B	0.88	-0.43	.	*	.	0.30	0.97
Ala	33	.	A	B	1.12	-0.41	*	*	.	0.30	0.86
Leu	34	.	A	B	.	.	.	C	0.53	-0.41	*	*	.	0.65	1.50
Ser	35	.	A	B	0.11	-0.34	*	*	F	0.45	0.54
Gln	36	.	A	B	0.82	0.14	*	.	F	-0.15	0.77
Glu	37	.	A	B	0.71	-0.36	*	.	F	0.60	1.83
Ile	38	.	A	B	0.60	-1.04	*	.	F	0.90	2.28
Thr	39	.	A	B	1.41	-0.64	*	*	F	0.90	1.14
Arg	40	.	A	B	0.90	-0.64	*	.	F	0.90	1.06
Asp	41	.	A	.	.	T	.	.	0.09	0.04	*	.	F	0.40	1.24
Phe	42	.	.	B	B	.	.	.	0.09	0.04	*	.	.	-0.30	0.71
Asn	43	.	.	B	B	.	.	.	0.12	-0.04	*	.	.	0.30	0.63
Leu	44	.	.	.	B	.	.	C	0.13	0.60	.	.	.	-0.40	0.28
Leu	45	.	.	B	B	.	.	.	0.02	0.99	.	.	.	-0.60	0.43
Gln	46	.	.	B	B	.	.	.	-0.19	0.20	.	.	.	0.04	0.47
Val	47	.	.	.	B	.	.	C	0.21	0.23	.	.	.	0.58	0.87
Ser	48	.	.	.	B	.	.	C	0.21	-0.07	.	.	F	1.82	1.42
Glu	49	T	C	0.81	-0.76	.	.	F	2.86	1.42
Pro	50	T	T	.	0.96	-0.73	.	.	F	3.40	2.95
Ser	51	T	T	.	0.10	-0.80	*	*	F	3.06	1.18
Glu	52	T	T	C	1.07	-0.54	*	*	F	2.37	0.51
Pro	53	.	.	.	B	T	.	.	1.12	-0.54	*	.	F	1.83	0.64
Cys	54	.	.	B	B	.	.	.	0.31	-0.21	*	.	.	0.64	0.75
Val	55	.	.	B	B	.	.	.	0.31	0.09	*	*	.	-0.30	0.36
Arg	56	.	.	B	B	.	.	.	0.72	0.51	*	*	.	-0.60	0.36
Tyr	57	.	.	B	B	.	.	.	-0.09	0.09	*	*	.	-0.15	1.30
Leu	58	.	.	B	B	.	.	.	-0.12	0.20	*	*	.	-0.15	1.45

Pro	59	.	.	B	B	.	.	.	-0.27	0.31	*	*	.	-0.15	1.16
Arg	60	.	.	B	B	.	.	.	0.59	1.00	*	*	.	-0.60	0.61
Leu	61	.	.	B	B	.	.	.	-0.41	0.24	*	*	.	-0.15	1.24
Tyr	62	.	.	B	B	.	.	.	-0.20	0.24	*	*	.	-0.30	0.56
Leu	63	.	.	B	B	.	.	.	0.61	0.31	*	*	.	-0.30	0.39
Asp	64	.	.	B	B	.	.	.	0.58	0.71	*	*	.	-0.60	0.76
Ile	65	.	.	B	B	.	.	.	-0.20	0.79	*	*	.	-0.60	0.76
His	66	.	.	B	.	.	T	.	-0.24	0.60	.	*	.	-0.20	0.49
Asn	67	.	.	B	.	.	T	.	-0.81	0.56	.	*	.	-0.20	0.22
Tyr	68	.	.	B	.	.	T	.	0.00	1.24	.	*	.	-0.20	0.26
Cys	69	.	.	B	.	.	T	.	0.04	0.56	.	.	.	-0.20	0.32
Val	70	.	A	B	B	.	.	.	0.12	0.06	.	*	.	-0.30	0.39
Leu	71	.	A	B	B	.	.	.	0.27	0.34	*	*	.	-0.30	0.21
Asp	72	.	A	B	B	.	.	.	0.27	-0.41	*	.	F	0.45	0.76
Lys	73	.	A	B	-0.19	-0.99	*	*	F	0.90	1.70
Leu	74	.	A	B	B	.	.	.	-0.38	-0.84	*	.	F	0.90	1.79
Arg	75	.	A	B	B	.	.	.	-0.11	-0.89	*	.	F	0.75	0.79
Asp	76	.	A	B	B	.	.	.	0.40	-0.39	*	.	.	0.30	0.40
Phe	77	.	A	B	B	.	.	.	0.19	0.00	*	.	.	0.30	0.65
Val	78	.	A	B	B	.	.	.	-0.07	-0.26	*	*	.	0.30	0.52
Ala	79	.	A	B	B	.	.	.	0.08	0.17	*	.	.	-0.30	0.48
Ser	80	.	A	.	B	.	.	C	-0.32	0.74	.	.	.	-0.40	0.30
Pro	81	T	C	-0.28	0.87	.	*	F	0.15	0.42
Pro	82	T	T	.	-0.43	0.23	.	.	F	0.65	0.83
Cys	83	T	T	.	-0.17	0.37	.	.	.	0.50	0.46
Trp	84	T	T	.	0.42	0.49	.	.	.	0.20	0.30
Lys	85	.	A	B	-0.13	0.46	.	.	.	-0.60	0.34
Val	86	.	A	B	0.08	0.67	.	.	.	-0.60	0.46
Ala	87	.	A	B	-0.01	0.10	.	.	.	-0.30	0.74
Gln	88	.	A	B	-0.16	-0.43	.	.	.	0.30	0.49
Val	89	.	A	B	0.18	0.26	.	.	.	-0.30	0.55
Asp	90	.	A	B	0.13	-0.39	.	.	F	0.60	1.09
Ser	91	.	A	B	1.03	-0.89	.	.	F	0.90	1.05
Leu	92	A	A	1.03	-1.29	*	*	F	0.90	2.83
Lys	93	A	A	1.14	-1.43	*	*	F	0.90	1.71
Asp	94	.	A	.	.	T	.	.	2.04	-1.43	*	.	F	1.30	2.50
Lys	95	A	A	1.23	-1.81	*	*	F	0.90	6.06
Ala	96	A	A	1.29	-1.81	*	*	F	0.90	2.50
Arg	97	.	A	B	1.79	-1.06	*	*	F	0.90	2.34
Lys	98	.	A	B	0.86	-0.57	*	*	F	0.90	1.69
Leu	99	.	A	B	0.26	0.11	*	.	.	-0.15	1.17
Tyr	100	.	A	B	0.21	0.23	*	.	.	-0.30	0.59
Thr	101	.	.	B	B	.	.	.	0.50	0.63	*	.	.	-0.60	0.48
Ile	102	.	.	B	B	.	.	.	-0.31	1.01	*	.	.	-0.60	0.77
Met	103	.	.	B	B	.	.	.	-1.02	1.11	*	.	.	-0.60	0.43
Asn	104	.	.	B	.	.	T	.	-0.10	0.93	*	.	.	0.04	0.16
Ser	105	.	.	B	.	.	T	.	0.26	0.44	*	.	.	0.28	0.44
Phe	106	.	.	B	.	.	T	.	0.57	-0.24	*	.	.	1.42	0.88
Cys	107	.	.	B	.	.	T	.	0.64	-0.86	.	.	.	1.96	0.91
Arg	108	T	.	.	0.39	-0.57	.	.	.	2.40	0.56
Arg	109	.	.	B	B	.	.	.	-0.31	-0.31	*	.	F	1.41	0.48
Asp	110	.	.	B	B	.	.	.	-0.82	-0.31	.	.	F	1.17	0.78
Leu	111	.	.	B	B	.	.	.	-0.93	-0.20	*	.	.	0.78	0.33
Val	112	.	.	B	B	.	.	.	-0.27	0.49	*	.	.	-0.36	0.14
Phe	113	.	.	B	B	.	.	.	-0.38	0.49	*	.	.	-0.60	0.14
Leu	114	.	.	B	B	.	.	.	-1.16	0.49	*	.	.	-0.60	0.28
Leu	115	.	.	B	B	.	.	.	-1.16	0.37	.	.	.	-0.02	0.20
Asp	116	T	T	.	-0.93	0.13	.	.	F	1.21	0.37
Asp	117	T	T	.	-0.89	-0.16	.	.	F	2.09	0.46
Cys	118	T	T	.	-0.19	-0.16	.	.	.	2.22	0.46
Asn	119	T	T	.	0.38	-0.84	.	.	.	2.80	0.48
Ala	120	.	A	B	0.98	-0.09	.	.	.	1.42	0.45
Leu	121	.	A	B	0.09	0.34	.	.	.	0.69	1.29

833

Glu	122	.	A	B	-0.12	0.46	.	*	.	-0.04	0.56
Tyr	123	.	A	B	-0.31	0.49	.	*	.	-0.32	0.86
Pro	124	.	.	B	B	.	.	.	-0.62	0.63	.	*	.	-0.60	0.77
Ile	125	.	.	B	B	.	.	.	-0.34	0.43	.	*	.	-0.60	0.64
Pro	126	.	.	B	B	.	.	.	-0.39	0.91	.	*	.	-0.60	0.59
Val	127	.	.	B	B	.	.	.	-1.20	0.80	.	.	.	-0.60	0.29
Thr	128	.	.	B	B	.	.	.	-1.17	1.06	.	.	.	-0.60	0.34
Thr	129	.	.	B	B	.	.	.	-0.96	0.80	.	.	F	-0.11	0.34
Val	130	.	.	B	B	.	.	.	0.04	0.37	.	.	F	0.53	0.75
Leu	131	.	.	B	.	.	T	.	0.26	-0.27	.	*	F	2.02	1.02
Pro	132	.	.	B	.	.	T	.	1.22	-0.36	.	*	F	2.36	1.23
Asp	133	T	T	.	1.14	-0.84	.	*	F	3.40	3.24
Arg	134	.	.	B	.	.	T	.	1.07	-1.06	.	*	.	2.51	5.03
Gln	135	.	.	B	1.53	-1.31	.	*	.	1.97	4.16
Arg	136	.	.	B	1.96	-1.31	.	*	.	1.63	3.18

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 440.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit

27 March 1997

Accession Number

97979

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

	For receiving Office use only			For International Bureau use only	
<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

ATCC Deposit No. 97979**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97979

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 442.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
04 April 1997

Accession Number
97974

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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ATCC Deposit No. 97974**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97974

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 442.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
29 May 1997

Accession Number
209080

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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ATCC Deposit No. 209080**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209080

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 444.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit

03 December 1997

Accession Number

209511

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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Authorized officer			Authorized officer		

ATCC Deposit No. 209511**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209511

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by an applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 448.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
04 April 1997

Accession Number
97975

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

For receiving Office use only

For International Bureau use only

☐ This sheet was received with the international application

☐ This sheet was received by the International Bureau on:

Authorized officer

Authorized officer

ATCC Deposit No. 97975**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97975

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 448.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
29 May 1997

Accession Number
209081

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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Authorized officer			Authorized officer		

ATCC Deposit No. 209081**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209081

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 454.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
04 April 1997

Accession Number
97976

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 97976**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97976

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 455.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
04 April 1997

Accession Number
97977

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

ATCC Deposit No. 97977**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97977

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 455.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
29 May 1997

Accession Number
209082

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

ATCC Deposit No. 209082**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209082

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 457.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
06 January 1998

Accession Number
209568

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer			Authorized officer		

ATCC Deposit No. 209568

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209568

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 458.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
07 April 1998

Accession Number
209746

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer			Authorized officer		

ATCC Deposit No. 209746

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209746

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by an applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 461.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
28 April 1997

Accession Number
209007

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 209007

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209007

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 461.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
29 May 1997

Accession Number
209083

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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ATCC Deposit No. 209083**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209083

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 465.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
18 May 1998

Accession Number
209877

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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Authorized officer			Authorized officer		

ATCC Deposit No. 209877**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209877

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
28 April 1997

Accession Number
209008

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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Authorized officer			Authorized officer		

ATCC Deposit No. 209008

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209008

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
29 May 1997

Accession Number
209084

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer			Authorized officer	

ATCC Deposit No. 209084**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209084

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
28 April 1997

Accession Number
209010

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

ATCC Deposit No. 209010**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209010

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

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SWEDEN

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NETHERLANDS

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
29 May 1997

Accession Number
209085

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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ATCC Deposit No. 209085**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209085

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

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SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 469.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
28 April 1997

Accession Number
209009

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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Authorized officer			Authorized officer		

ATCC Deposit No. 209009

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209009

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 475.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
28 April 1997

Accession Number
209011

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

For receiving Office use only

For International Bureau use only

☐ This sheet was received with the international application

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Authorized officer

Authorized officer

ATCC Deposit No. 209011**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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ATCC Deposit No.: 209011

UNITED KINGDOM

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DENMARK

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SWEDEN

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NETHERLANDS

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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- 5 (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
- (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
- 10 (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
- (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
- 15 (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;
- (f) a polynucleotide which is a variant of SEQ ID NO:X;
- (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
- (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
- 20 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.
- 25
2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.
- 30

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence
5 included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to
10 SEQ ID NO:X.
5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
15
6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
20
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
25
9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.
30
11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
- 5 (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (e) a secreted form of SEQ ID NO:Y or the encoded sequence
- 10 included in ATCC Deposit No:Z;
- (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- 15 (i) a species homologue of the SEQ ID NO:Y.
12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
- 20 13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
- 25 15. A method of making an isolated polypeptide comprising:
- (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
- (b) recovering said polypeptide.
- 30 16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

5 18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

10 (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

15 (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20 20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

25 21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

Figure 1A

1 AATTCGGCACGAGGGAAATTCAAGCACTTTTCTCTAAAAGAAGGGGAATGGATGCTGAAA 60

61 CAACACGTTTCCCAAAAGGGAGCAGACACTGGGCTTGTGAAGCTGCCCCATACCTTCCC 120

121 CACAGAACTGGGGTCCGGCCTCCCTGACATGCAGATTTCCACCCAGAAGACAGAGAAGGA 180

181 GCCAGTGGTCATGGAATGGGCTGGGGTCAAAGACTGGGTGCCTGGGAGCTGAGGCAGCCA 240

241 CCGTTTCAGCCTGGCCAGCCCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCTAC 300

301 CATGCGGACACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCTGTTCACTACTAC 360
1 M R T L F N L L W L A L A C S P V H T T 20

361 CCTGTCAAAGTCAGATGCCAAAAAGCCGCTCAAAGACGCTGCTGGAGAAGAGTCAGTT 420
21 L S K S D A K K A A S K T L L E K S Q F 40

421 TTCAGATAAGCCGGTGCAAGACCGGGGTTTGGTGGTGACGGACCTCAAAGCTGAGAGTGT 480
41 S D K P V Q D R G L V V T D L K A E S V 60

481 GGTTCCTTGAGCATCGCAGCTACTGCTCGGCAAAGGCCCGGgaCAGACACTTTGCTGGGGa 540
61 V L E H R S Y C S A K A R D R H F A G D 80

541 TGTACTGGGCTATGTCACTCCATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTGG 600
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601 GAGCAAGTTTACACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGTGGCCGTGAGAT 660
101 S K F T Q I S P V W L Q L K R R G R E M 120

661 GTTTGAGGTACGGGCCTCGACGACGTGGACCAAGGGTGGATGCGAGCTGTCAGGAAGCA 720
121 F E V T G L H D V D Q G W M R A V R K H 140

721 TGCCAAGGGCCTGCACATAGTGCCTCGGCTCCTGTTTGAGGACTGGACTTACGATGATTT 780
141 A K G L H I V P R L L F E D W T Y D D F 160

781 CCGGAACGTCTTAGACAGTGAGGATGAGATAGAGGAGCTGAGCAAGACCGTGGTCCAGGT 840
161 R N V L D S E D E I E E L S K T V V Q V 180

Figure 1B

841	GGCAAAGAACCAGCATTTCGATGGCTTCGTGGTGGAGGTCCTGGAACCAGCTGCTAAGCCA	900
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901	GAAGCGCGTGACCGACCAGCTGGGCATGTTACGCACAAGGAGTTTGAGCAGCTGGCCCC	960
201	K R V T D Q L G M F T H K E F E Q L A P	220
961	CGTGCTGGATGGTTTCAGCCTCATGACCTACGACTACTCTACAGCGCATCAGCCTGGCCC	1020
221	V L D G F S L M T Y D Y S T A H Q P G P	240
1021	TAATGCACCCCTGTCCTGGGTTCGAGCCTGCGTCCAGGTCCTGGACCCGAAGTCCAAGTG	1080
241	N A P L S W V R A C V Q V L D P K S K W	260
1081	GCGAAGCAAAATCCTCCTGGGGCTCAACTTCTATGGTATGGACTACGCGACCTCCAAGGA	1140
261	R S K I L L G L N F Y G M D Y A T S K D	280
1141	TGCCCCGTGAGCCTGTTGTCTGGGGCCAGGTACATCCAGACACTGAAGGACCACAGGCCCCG	1200
281	A R E P V V G A R Y I Q T L K D H R P R	300
1201	GATGGTGTGGGACAGCCAGGYCTCAGAGCACTTCTTCGAGTACAAGAAGAGCCGCAGTGG	1260
301	M V W D S Q X S E H F F E Y K K S R S G	320
1261	GAGGCACGTCTTCTACCCAACCTGAAGTCCCTGCAGGTGCGGCTGGAGCTGGCCCCG	1320
321	R H V V F Y P T L K S L Q V R L E L A R	340
1321	GGAGCTGGGCGTTGGGGTCTCTATCTGGGAGCTGGGCCAGGGCCTGGACTACTTCTACGA	1380
341	E L G V G V S I W E L G Q G L D Y F Y D	360
1381	CCTGCTCTAGGTGGGCATTGCGGCCTCCGCGGTGGACGTGTTCTTTTCTAAGCCATGGAG	1440
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Figure 2

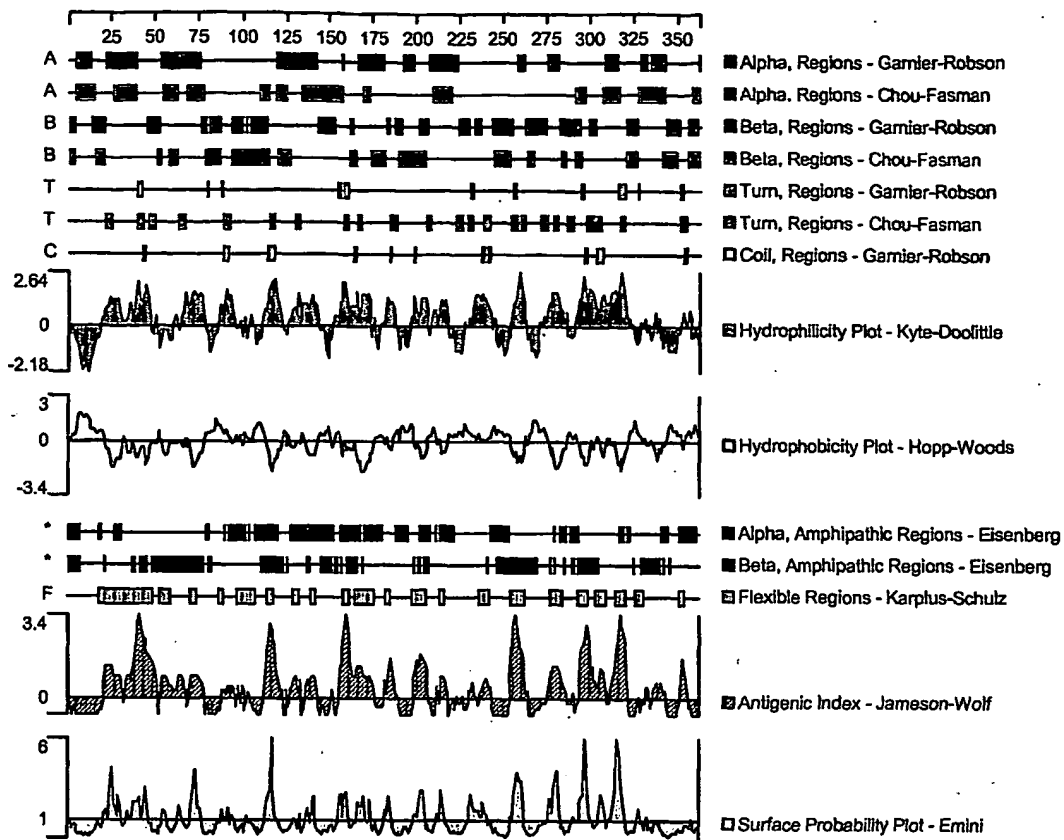


Figure 3A

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121	CAGGGAGCCGGCCGGAAGCGCGATGGGGCCCCAGCCGCTCGCTCCTGCTCCTGCTCC	180
1	M G A P A A S L L L L L L	13
181	TGCTGTTTCGCCTGCTGCTGGGCGCCCGGGGGCCAACTCTCCAGGACGGCTACTGGC	240
14	L F A C C W A P G G A N L S Q D G Y W Q	33
241	AGGAGCAGGATTTGGAGCTGGGAACTCTGGCTCCACTCGACGAGGCCATCAGCTCCACAG	300
34	E Q D L E L G T L A P L D E A I S S T V	53
301	TCTGGAGCAGCCCTGACATGCTGGCCAGTCAAGACAGCCAGCCCTGGACATCTGATGAAA	360
54	W S S P D M L A S Q D S Q P W T S D E T	73
361	CAGTGGTGGCTGGTGGCACCCTGGTGCTCAAGTGCCAAGTGAAAGATCACGAGGACTCAT	420
74	V V A G G T V V L K C Q V K D H E D S S	93
421	CCCTGCAATGGTCTAACCCTGCTCAGCAGACTCTCTACTTTGGGGAGAAGAGAGCCCTTC	480
94	L Q W S N P A Q Q T L Y F G E K R A L R	113
481	GAGATAATCGAATTCAGCTGGTTACCTCTACGCCCCACGAGCTCAGCATCAGCATCAGCA	540
114	D N R I Q L V T S T P H E L S I S I S N	133
541	ATGTGGCCCTGGCAGACGAGGGCGAGTACACCTGCTCAATCTTCACTATGCCTGTGCGAA	600
134	V A L A D E G E Y T C S I F T M P V R T	153
601	CTGCCAAGTCCCTCGTCACTGTGCTAGGAATTCCACAGAAGCCCATCATCACTGGTTATA	660
154	A K S L V T V L G I P Q K P I I T G Y K	173
661	AATCTTCATTACGGGAAAAAGACACAGCCACCCTAAACTGTGAGTCTTCTGGGAGCAAGC	720
174	S S L R E K D T A T L N C Q S S G S K P	193
721	CTGCAGCCCGGCTCACCTGGAGAAAGGGTGACCAAGAACTCCACGGAGAACCAACCCGCA	780
194	A A R L T W R K G D Q E L H G E P T R I	213
781	TACAGGAAGATCCCAATGGTAAACCTTCACTGTCAGCAGCTCGGTGACATTCCAGGTTA	840
214	Q E D P N G K T F T V S S S V T F Q V T	233
841	CCCGGAGGATGATGGGGCGAGCATCGTGTGCTCTGTGAACCATGAATCTCTAAAGGGAG	900
234	R E D D G A S I V C S V N H E S L K G A	253

Figure 3B

901 CTGACAGATCCACCTCTCAACGCATTGAAGTTTTATACACACCAACTGCGATGATTAGGC 960
254 D R S T S Q R I E V L Y T P T A M I R P 273

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1021 ATCCAGTCCCCCAGCAGTACCTATGGGAGAAGGAGGGCAGTGTGCCACCCCTGAAGATGA 1080
294 P V P Q Q Y L W E K E G S V P P L K M T 313

1081 CCCAGGAGAGTGCCCTGATCTTCCCTTTCCTCAACAAGAGTGACAGTGGCACCTACGGCT 1140
314 Q E S A L I F P F L N K S D S G T Y G C 333

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334 T A T S N M G S Y K A Y Y T L N V N D P 353

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374 I V F L L L I M L I F L G H Y L I R H K 393

1321 AAGGAACCTACCTGACACATGAGGCAAAAGGCTCCGACGATGCTCCAGACGCGGACACGG 1380
394 G T Y L T H E A K G S D D A P D A D T A 413

1381 CCATCATCAATGCAGAAGGCGGGCAGTCAGGAGGGGACGACAAGAAGGAATATTTCATCT 1440
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1621 GGAGGGAGGAGGGCGGGGGAGGGGAGGGTTGCCCTCAGCCCTTCCGTGGCTTCTCTGC 1680

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1801 GGAGGAGAGTGAAGGTAGAGGGGTGAGGAAGGGTAAGGGGCAGGGCTGGTTTCAGCTGGG 1860

Figure 3C

1861 GGCTCTCACCAGCCCTCCTTTCAGCCTCTACAACAGAGCAGCTTCCCAGACTTCTCCAGG 1920
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1981 ACACCTGAGCACTACGGACAGGGAGGCAGGTGCCACCTTGACACCTCTCTCCATAGCAA 2040
2041 TGGGAAAGTGATGAGTGCGGGAGTCCTGAGGAGATGTGGCCTGCAGACAACATGCAGCCA 2100
2101 TGCAGGGACCCAGGACTGTAACCTGGGGAGGACGCGGGTCCCTGCAAGGAAGAGTAGATT 2160
2161 TGGAGAGGAAGGATGGAGGTGGACTCTCACCCCATTCCTCCGGAAATGAACAAAGCCGG 2220
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Figure 4

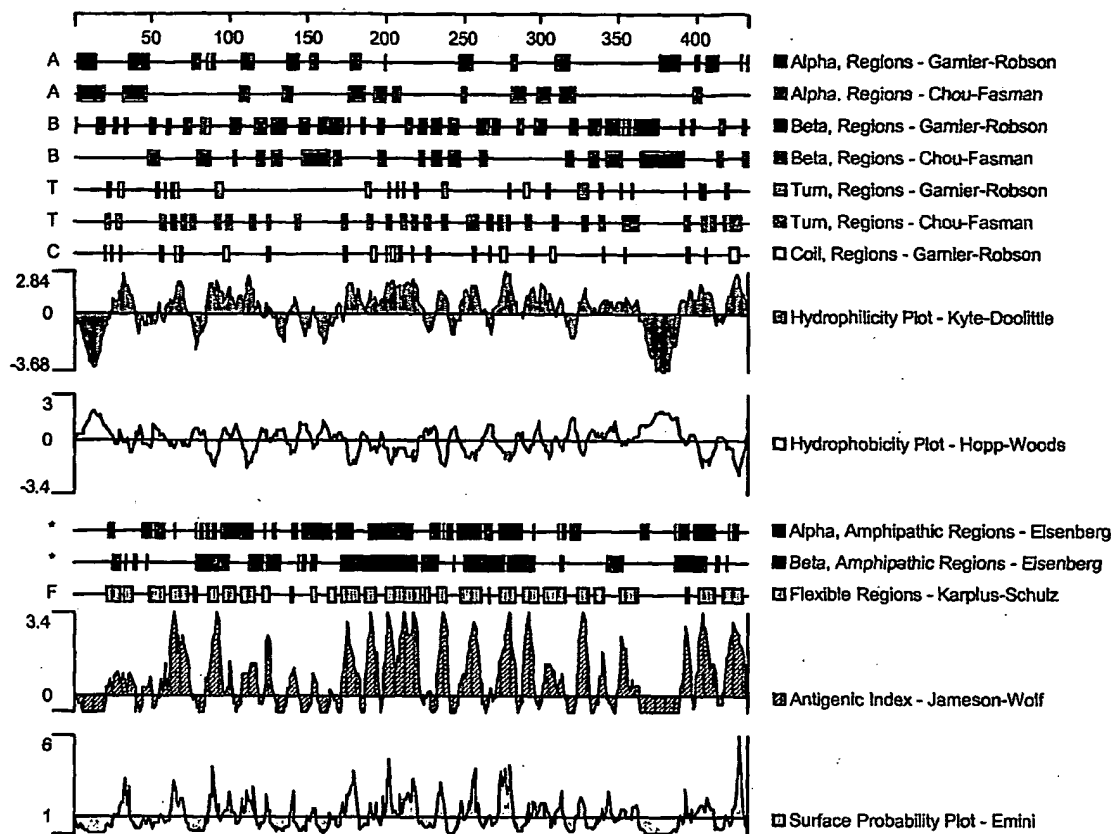


Figure 5A

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181 ACCTGCCCAG GCTGTACCTG GACATACACA ATTACTGTGT GCTGGACAAG CTGGGGGACT 240
57 Y L P R L Y L D I H N Y C V L D K L R D 76

241 TTGTGGCCTC GCCCCCGTGT TGGAAGTGG CCCAGGTAGA TTCTTGAAG GACAAAGCAC 300
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361 ACTGCAATGC CTTGGAATAC CCAATCCCAG TGACTACGGT CCTGCCAGAT CGTCAGCGCT 420
117 D C N A L E Y P I P V T T V L P D R Q R 136

421 AAGGGAAC TG AGACCAGAGA AAGAACCCTA GAGAACTAAA GTTATGTCAG CTACCCAGAC 480

Figure 5B

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541 GTATCTCTCT ACCTTCTGGA AACAGGGCT GGTATTCCTA CCNGGAACC TCCTTGAGC 600

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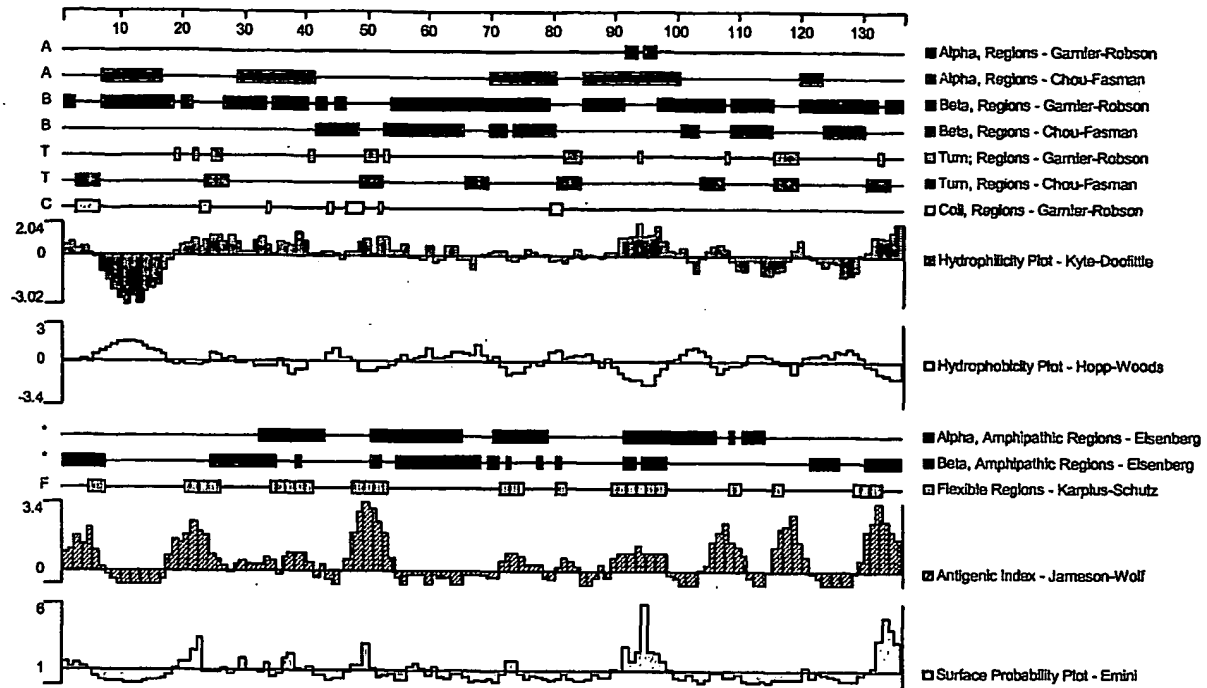
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Figure 6



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<223> n equals a,t,g, or c

<400> 12

cactgcacca	gctttgttat	ctgtaaaatg	atgataatac	caacaccttc	ttcttggggg	60
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aacatgtaat	gaatgtagta	atagtaatta	ttttattttc	ttttgattca	gttgggacta	180
tgttcagctg	taacagaata	cccaaaataa	ctgtttttaa	caaattaaag	tttwgttggtg	240
aagttttgtt	acgaattcag	acaatccagg	gcttttatag	atgcaccagg	atcagcaggt	300
acaaaggcat	ctttcctgat	ttctgccagt	ctcaatgcac	gggttgcaat	ccagartcca	360
rgatggcagt	tccagccctg	gttacgccc	tatttagcaca	cagaaagaaa	gagaaaggga	420
tgtgcctctt	cactttaatc	atagctccca	ctagatgcac	ccactacttc	tgctgatact	480
ccattagcta	atgcttgctt	acatgggtcac	acttagtttc	cagagagaca	tgtctggaca	540
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ttgcttggtt	gcattcctct	tagcataagc	cacattcttt	ttatgaagtt	gtcctcagtt	660
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ttcttttgtc	atcagcacca	tcactaccac	tgccytcttc	aaagccacca	cgttctgtcc	780
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cagagtaagc	ttttgaaaat	gtaggtcaga	tcatgtctct	ctcttctctt	tcaaaacctt	900
cccgatggct	tttcatatta	ctcaaaagaa	aacctaaaac	tttgtgtgta	gatctatgtg	960
accgggctta	ttcttctctt	tactttatct	ctgtattgct	cttctcactt	ctactccagc	1020
catcccacct	ccttgctgct	tgtcctatac	tcctaaaaga	agttcagttt	tcccttatga	1080
tatttgcact	taaaatagaa	aaaaaaaaaa	aaaaaaaaact	cgaggggggc	c	1131

<210> 13

<211> 941

<212> DNA

<213> Homo sapiens

<400> 13

ggcacgagta	gcatttcatt	taatctgcag	gtatattctc	ccaacagttt	attgtcatgt	60
gatgtcctca	gccaagattg	traggcagag	aggagctgtc	ccaacctact	ataccaccga	120
ggctggagag	atcatatttt	tggattttaa	ctggagtctc	tccatccttc	acattgttga	180
gtcctctgt	agcaaaccgg	aaaagtcagt	gacagaagat	gccgctagcg	gtttgagcca	240
gagaatgaca	gctctgggtt	ggagaaaagg	gccggatggg	ggctctagaa	agcccatcct	300

tctgctcttc	ttttttctcc	cccttatatt	gtgctttcat	tcattcatte	attcatcaaa	360
catttggtga	gcacctatta	tgtgtcaagc	tctgtgctag	cctctggaaa	acctgcccctc	420
atgtagctca	ctgtggagta	ggagaaacaa	tgactacact	atgataagca	cgggttggtca	480
gggtctcaca	gagcagtggc	ccctcatcca	gaccgatgag	gtcaaagaag	gcatccagggc	540
gaggatgggtg	tcagagctaa	ctgaagaatg	agagggagct	gcaccascag	gggttggaac	600
tgaaggtggc	agtgccctga	gtcttgattc	cagcagaggg	agagcagtct	gtgaaaaggc	660
accaaggggtg	ggagagggca	gagcacatgg	aggaacttca	ggtagttctg	gatggcscgt	720
gggcaaagct	agagaggtaa	gaagaatcta	caaagtgtcc	tcgagttaca	tgaacttcca	780
tcccaataaa	cccattggaa	acgaaaaatt	taagtccagaa	gtgcatttaa	ggctgggtccg	840
agtagaatga	tttttacaa	gaattgatca	caaccagtta	cagatgtctt	tgctccttct	900
ccactccac	tgcttcacct	gactagcctt	taaaaaaaaa	a		941

<210> 14

<211> 843

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (19)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (87)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (89)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (525)

<223> n equals a,t,g, or c

<400> 14

cnagggataa	ccccaaagnt	gggaaataaa	ccctcaatta	aagggggaac	caaaaagctg	60
ggaagttccc	ccccgcggtg	gcggccngnt	ctaggaacta	gtggaatccc	ccggggctgc	120
agggaattcg	gcacggagtg	ggaatgttgt	ttgtatgata	ctattttccac	aawatgcatt	180
gagacttggg	ktgtggccta	ggacatggtc	aattcttityt	aaatattccg	tgaatttctt	240
tagtgcata	tctccgatgg	gggctgtggg	gacagagttc	taaataatgcc	cattagatta	300
aatctcttca	ttctgttgct	cacatcttct	atatccttat	taatctgtca	atctcttcaa	360
gagaggtggt	attaaaatct	ctcactgtat	gtgtcacttt	gcccttaaaa	ttctgatgat	420
ttgctttata	aatggttata	accattttcc	aggaagaaca	ttaaagaact	ttccattggc	480
attatccagt	ttccctcaaa	atactggttt	tttttatatt	ggctnctaag	cagctatgaa	540
tccagtttct	cagaagccct	tgtctcaagg	catttgtttc	cagattacct	tgtagcatc	600
cacactatgg	gctattttag	aaaaacaaaa	aaagtatcaa	aatcatatag	ctatgatttt	660
cctgtgcttg	aaggagcctt	aaagctcatc	tagtccagcc	agtatttggt	catccaaatt	720
ctgccaaagaa	atctctattg	tcaagatatt	ctttaccatc	tttgggacat	tctcattatt	780
agaaacaaat	cctaagaaga	aattctgcca	takacaaccc	atccgttctt	taaaaaaaaa	840

aaa

843

<210> 15

<211> 1018

<212> DNA

<213> Homo sapiens

<400> 15

ctgtaatttt	taattttcat	ataccgtgct	ttgattctaa	ttttatTTTT	tgagttctct	60
gaaggttaca	tatacagagt	gcttcaggaa	tgatcatttt	gttattattc	atgcttctta	120
acaatgttgt	tttagtccaa	gaagataatt	gccagagaaa	gaatacagtg	caggaaagaa	180
gargctggag	ccagtgggtga	agarggattg	agargacaga	cattgtggga	atgaaatcat	240
gaataatcgt	gtttttgaat	tgtccaaaaa	cttctacaaa	ccatgaaatg	ttggagttaa	300
aatctaattg	ttgaaaaatt	ccccacattc	cttgtatccc	ttaggttgag	cataattcca	360
catccgtgga	ctgatgcact	tccaagagg	gggcctcatt	aactcttccg	aggcagcagc	420
agcaagggca	ccccctcctt	tccccccaca	cccayttct	catggctcct	ctttctctca	480
tctcatgctt	agggttagaaa	agggcacaa	gtaaggaagc	ccttgggaat	aggctgaatc	540
tggtatctta	atgttggtgcc	aaatacttaa	tggtgcttga	tttaaaaaa	gcaaactatg	600
agaaaggtaa	ttataattat	gaggccagtt	ctttaagcta	gctttttttc	ccctctcaaa	660
cagcatattg	gcttggatgt	cagcaggaga	aagtgttttt	tgcaatacac	ataatgcata	720
tatggtcctg	ttagcaatct	atagaaaata	gatattgctc	attaaggtaa	atatttttgt	780
tgatgaatga	tctggaatgg	tctggacttg	ttgtgtgaac	aggaaattgc	tctgtaggct	840
ttgacttgtg	aggtaaagag	tgaggctggg	aagattaatt	aaagtaaata	ctgtgacaat	900
aggatgtcaa	aacccaaaaa	gtgtttctga	aactcaagga	attaatgaca	catagggaag	960
tttttgccat	attaagcata	gagtaggaga	ggcaagtcaa	gaataaaaaa	aaaaaaaa	1018

<210> 16

<211> 661

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (478)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (661)

<223> n equals a,t,g, or c

<400> 16

tttaagaaat	tagtgaatcc	ccgngtgcag	ggaattcggc	acgaggagga	ggccgtcagc	60
tggcaggagc	gcaggatggc	agctgytccc	ccgggttgca	ccccccaggy	tctgctggac	120
ataagytggg	taacagagag	cctgggagct	gggcagcctg	tacctgtgga	gtgccggcac	180
cgcctggagg	tggctggggc	aaggaagggg	cctctgagcc	cagcatggat	gcctgcctat	240
gcctgccagc	gccctacgcc	cctcacacac	cacaacactg	gcctmtccga	gctgctggag	300
catggagtgt	gtgaggaggt	ggagagagtt	cggcgctcag	agaggtaacca	gacctgaag	360
gtgctgcagg	cagggtctcg	acctacccca	ggaatgtcct	gccctgggaa	tgacaacaca	420
gtccacacca	tgcacgggga	ggcaaacagg	ggcagctgac	ccagcccagg	ggtcaganga	480
ggtcttgccg	aggaagtggc	agctaagctg	atacctgata	tgacacwagkc	agccargygg	540

agacaggcaa	ggaagaagct	tgttttgagg	acagaatttt	ctagatcact	cagcaccatc	600
tggtcttttg	ggctttttgt	tttattttgt	ttttgagacg	gggtctcgct	ctgtcgccca	660
n						661

<210> 17

<211> 553

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (507)

<223> n equals a,t,g, or c

<400> 17

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tcttctcagc	tgtcagacgg	cttgctgctt	gttttccaca	ccaccatgtc	tattcctttgc	120
tgtccttwac	tctgcctgtt	tttttccttt	tgtatttctt	ctggctcttg	tcccttttcc	180
cagtgctwc	agcttttctt	tattgccact	ttcagtcaga	gcagtcctgt	gcttctgggtg	240
ccggcataca	atacttactt	gagtttcttg	gcttttcttg	actgtgcac	tcttacttca	300
acataggaat	agcctgtcat	agaatttctc	cagttccagg	gctcaagagg	gagagtgccca	360
gaaaattgag	actgttttcc	ctgtcttgga	ttgaattcat	aaagcaaaac	cagtgtttgt	420
gtgaggggtt	gctgtgtcat	gcctataggt	tggttggggtg	caaacctata	gaatccagcc	480
tgcgaaaaga	aagraaccag	agaatanacg	catcagaaca	atgcttgaca	tcatttctca	540
atcaagcagt	cca					553

<210> 18

<211> 869

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (635)

<223> n equals a,t,g, or c

<400> 18

ggcacagagct	gccaacactg	aggctttcgt	ggcttctcac	atctagatgt	atccctctca	60
aattctatcct	ctatccaggc	accagattga	ggatatctaaa	atgtcaactt	tccagttact	120
ccttcttata	ctagcccaat	caacttaca	gataaagtcc	aagccccttc	atatgacaaa	180
ccacaccctg	cttaactctc	caggtttgaa	tccttcatct	cctactttta	actttaaaac	240
ccagcagcac	gaaagtgtct	cctatgcatg	ttgccatag	cgttctctcc	atcatgcatt	300
tgcttgagca	agatgtcttg	agttaacatc	ttattcttta	agactcattg	tggtggtaga	360
cagccttta	taacggatcc	ttggccaggc	acagtgactc	acacctgtaa	tcccagaact	420
ttgaaaggcc	aaagaaggaa	gaaagcttga	ggccagtagt	ttgagaccag	cctgggaaac	480
agagagatat	cccatctgta	caaaaaattt	aaaaaaatat	tagcaggagg	tagtggcatg	540
cacaagtggg	cccagctcca	tgggagastg	aggtaggaac	atcacttgag	cccagggaag	600
caaggctgca	gtgaaccatg	atcagaacat	tgcantccag	cttgggtaac	agagtggagac	660
cttaggtcag	aaaaatgaat	aaataagcat	aaaattttta	aaacttagcc	aggcatgggtg	720
gcacacatct	gtgggtccctg	ctacttagga	ggctgagggtg	agaggatcct	tgagcccagg	780
aggccaacac	tacagtggag	tatgattgtg	ccactaaact	ccaacctggg	tgaaaaagca	840
aaaccctgcc	aaaaaaaaaa	aaaaaaact				869

<210> 19

<211> 959

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (930)

<223> n equals a,t,g, or c

<400> 19

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aaaaaaaaaa	aattataata	ctatatgcca	taaaatgaca	tttcatat	aaagagtttt	120
ttaaaactct	tgtattcaca	tgccataatt	tgaaacccta	tttactgaa	tgagaatggt	180
atctgtgtgc	ctcatttttt	cattttttatc	cttaacaatt	tccaccacag	ccagtgcata	240
taatggcaat	gacaccag	gatggaatga	taagttccat	crcmgctcag	tcaagacgca	300
gacttgatgt	ggccccaaca	acagtcaata	atggagtctc	caaaataaag	ctctatagga	360
aaggtaaata	cccgtgcac	aagaaaccac	agcatctagg	ttctaacccc	atctctatga	420
agagcttgct	gggagagttt	tgacattwaa	caatctgtct	gatkgccaat	tttyttcttc	480
tataaaatga	taatgttkga	ytcaaagatc	caaagtcaat	tcatgggtcta	aaacttaatg	540
atTTTTTTtag	gttttggkac	atttcactgt	acactgtagt	aatttatatc	ttattttccc	600
actaatTTtag	aaaaatatyt	aaatgatcct	taattggcaa	tgggtcctaa	gaattttgtt	660
ttaaatccct	gttacccaaa	agagcccttt	tttgtatctc	gcagtagtta	caaggatctt	720
tctaaatctt	aaaaaaaaaa	aaaaaagaaa	gaaagaaaag	aaaagaaaaa	aagtcagccg	780
ggcgtggtgg	ctcatgcctg	taatcccagc	actttgggac	caaggtggac	agatcacgag	840
gtcaggagat	ggagaccatc	ccggccaaca	tggagaaacc	ctgtctctac	taaaaaaaaa	900
aaaaactcga	ggggggcccg	gtacccaatn	cgccggctag	tggtcgtaaa	acaatcaaa	959

<210> 20

<211> 1446

<212> DNA

<213> Homo sapiens

<400> 20

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cagtcaacac	tttcttgctc	cctgttttct	cttctgtggg	atgatctcag	atgcaggggc	120
tgggttttggg	gttttcctgc	ttgtgccaa	ggctggacac	tgctgggggg	ctggaaagcc	180
cctcccttcc	tgccctctgc	tgccctccat	ccctccatgg	gtgctgccat	ccttccctgga	240
gagaggggag	tgaaagctgg	tgtgagccca	gtgggttccc	gccactcac	ccaggagctg	300
gctggggccag	gacggggaga	gggagcactg	ctgcccctcc	ggccctgctc	cttccgcagt	360
taggggtgga	ccgagcctcg	ctttccccac	tggtctggag	ggaaagggaa	ggaggggggtc	420
ttcaggctgg	agccaggctg	gggggtgctg	gtggagagat	gagatttagg	gggtgcctca	480
tgggggtggc	aggcctgggg	tgaaatraga	aaggcccaga	acgtgcaggt	ctgaggagg	540
gaagtgtcct	gagtgaagga	ggggaccccc	atcctggggg	atgctgggag	tgagttagtg	600
agatggctga	gtgaggggta	tggggagcct	gaggttttat	gggcctgtgt	atcccttct	660
cccgcccca	gcctgcctcc	ctcctgccc	cctggcccac	aggtctccct	ctggtccctg	720
tccctctgg	ggttggggat	ggagcggcag	caaggggtgt	aatggggctg	ggttctgtct	780
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ggtagcgggt	gggtggggccc	tccttgagg	tctggggcca	ggctttggct	ctgctgcctc	900
tcagtcacca	agtcacactc	ctctgaaaat	ccagtcctct	ctttggatgt	ccttgtgagt	960
cactctgggc	ctggctgtcg	tcctctctca	gcttcttgtt	cctgggacaa	gggtcaagcc	1020
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tttgcggggg	gcagggcaga	aatggactcc	ttttgggtcc	ccgaggtggg	gtccctccc	1140
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cgtgtggtgg	cgcctggcac	tcagggaccc	ccagctgccc	cagccctggg	ctctggcgca	1260
tctcttccct	cttgtcccca	agatctgcgc	ctctagtgcc	ttttgagggg	ttcccatcat	1320
ccctccctga	tattgtattg	aaaatattat	gcacactggt	catgcttcta	ctaatacaata	1380
aacgctttat	ttaaagccaa	aaaaaaaaaa	aaaaaactcg	agggggggcc	cgtacccaat	1440
tcgcca						1446

<210> 21
 <211> 1471
 <212> DNA
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (1470)
 <223> n equals a,t,g, or c

<400> 21
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 agtcttatga tgttggttgg caaggctaga taaaaagatg ttagaatgaa agaacatatt 120
 tttagtata tgtaaatgaa ggattctaca atagtcatat atttttatat gaatgaatgt 180
 tgggttgggc tggagaggta tgtgtgtgta aatataaagg tctcacattc agagtatagc 240
 tctgaaataa tggaaactcat gtctacaatt caacatgcat ctgtatagtt acatctcatg 300
 taaatataca cagacatatt ttgcagccag taattgacag ttaatgtcca aaacagggtga 360
 ttgataggta acagaaatta gataaccacc aattttgccc aagagaaaga ctagaaggac 420
 taaaagcagt tgaatgtatg gtactgacat tgtcataagc agtctgataa ccagtttatt 480
 gaaacgtgtg cattaacaga gaatttaatt ttaaaccat aatttctcct atccattaaa 540
 atattataat tgtagtagt atgaaaccaa caggaaatgt tttttaatca tttagttagg 600
 tgattcattt gtttcatggg caaacactat ccaggaaaag ccttgcttgc ctgtttccca 660
 aagagctcta agaaatagaa tcaagtgtaa aatgggttcag accattcagg atttcttgct 720
 actcttctca accccgatct tcctgttatt actgatgttt gaaaccctgt cattagcccc 780
 ggccctggta aagcccctca gagtcacctc tcattcatag caatagaatt caaccccaag 840
 tgggtgatgg tgtccccagc acagccgaga gacctgatct ctggattcag tgcttttagc 900
 tcttcagatt taccctaaga taccttcggg caatattttt aaccaaccca aaagctcttc 960
 aggtcatttc tgaagaggac aaggtgaatc ttggcttgga acaccatttt tgggctcttg 1020
 ctactgaatg aatcagaaag gaattttttc tgaagagcat tagaaagtaa aggagatgtt 1080
 aaaataagtt cttgaagtat gttttatatt tatctaaac actgatttta aaagtttaca 1140
 ttcaaatgtg tattcaaaag aagtactgat ttgtaattat tatagtttgt gtgtatcatc 1200
 cccttttaac cgtgcctaac aactgtactt aaattttgtt ttcctagtgt aacaaatgtt 1260
 tcccataaga ttttctagag ccaataaatg ggagtgaaaa attccttaag tggtatataa 1320
 gaaaatatat tagaaaatca gctttggatt atacgatttc taaaatatac taatacagaa 1380
 tcctcagtaa tatgttttga attggatttt ttctcagaac tgttacataa taaataatac 1440
 atcaaccaga aaaaaaaaaa aaaaaaattn c 1471

<210> 22
 <211> 1402
 <212> DNA
 <213> Homo sapiens

<400> 22
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 catgagctgc cagagctgac ggcggagagt ttggaagcag gtgacagtaa ccaattttgc 120
 tggaggaacc tottttcttg tatcaatctg cttcggatct tgaacaagct gacaaagtgg 180
 aagcattcaa ggacaatgat gctgggtggtg ttcaagtcag ccccatctt gaagcgggcc 240
 ctaaaggtga aacaagccat gatgcagctc tatgtgctga agctgctcaa ggtacagacc 300
 aaatacttgg ggcggcagtg gcgaaagagc aacatgaaga ccatgtctgc catctaccag 360
 aaggtgcggc atcggctgaa cgacgactgg gcatacggca atgatcttga tgcccgccct 420
 tgggacttcc aggcagagga gtgtgccctt cgtgccaaaca ttgaacgctt caacgccccg 480
 cgctatgacc gggcccacag caacctgac ttccctgccag tggacaactg cctgcagagt 540
 gtccctgggc aacgggtgga cctccctgag gactttcaga tgaactatga cctctgggtta 600
 gaaagggagg tcttctccaa gccatttcc tgggaagagc tgctgcagtg aggctgttgg 660
 ttaggggact gaaatggaga gaaaagatga tctgaaggta cctgtgggac tgtcctagtt 720

10

cattgctgca	gtgctcccat	ccccaccag	gtggcagcac	agccccactg	tgtcttcgc	780
agtctgtcct	gggcttgggt	gagcccagct	tgacctcccc	ttggttccca	gggtcctgct	840
ccgaagcagt	catctctgcc	tgagatccat	tcttccttta	mttcccccam	cctcctctct	900
tggatatggg	tggttttggc	tcatttcaca	atcagcccaa	ggytgggaaa	gctggaatgg	960
gatgggaacc	cctccgccgt	gcacttraat	ttcaggggtc	atgctgatgc	ctctcgagac	1020
atacaaatcc	ttgcctttgt	cagcttgcaa	aggaggagag	tttaggatta	gggccagggc	1080
cagaaagtcg	gtatcttggg	tgtgctctgg	gggtgggggtg	gggtgtttct	gatgttatct	1140
cagcctcctg	ctacattata	tccagaagta	attgcggagg	ctccttcagc	tgctcagca	1200
ctttgatttt	ggacagggac	aaggtaggaa	gagaagcttc	ccttaaccag	aggggccatt	1260
tttccttttg	gctttcgagg	gcctgtaa	atctatat	aattctgtgt	gtattctgtg	1320
tcagtgtggg	gtttttaatg	tgattgtgta	ttctgtttac	attaaaaaga	agcaaaaaata	1380
ataaaaaaaaa	aaaaaaaaaa	ct				1402

<210> 23

<211> 1047

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (301)

<223> n equals a,t,g, or c

<400> 23

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ccatctttcc	atcttggcct	cctaaagtgc	tgggactgca	ggcatgagcc	accatgccca	180
gccaagattc	ttattgatta	ccatgttgct	tcaagaagcc	aagccagttt	ccaatattcc	240
ccatttgctg	gagcttgggt	actttgggta	gaagcaactg	gtaaatgtgt	aattggaaca	300
nttgggtggg	tagataacca	cgtatggcca	aacctagagc	atctaggctc	acaattacta	360
tcctgacttg	ataacaagt	ttctgatatt	aacctgaaaa	tgggaataat	gccaaatctg	420
tgtaacttaa	catctatata	cacagtgggg	agaactgaag	ttattaaacc	tggaatctct	480
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gtcatattct	ttaaggacgt	gttctgaaac	tatatcaagc	atctggtttc	cacgtatttc	600
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tccttatgtg	tctaataaat	cttgttccat	gaaatgatca	aaaaaaaaaa	aaaaaaaaact	1020
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<210> 24

<211> 990

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (834)

<223> n equals a,t,g, or c

<400> 24

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taccactcca	aatccaaagc	aatgaacagt	cttttctgga	tgatttttatt	gcctgtgtcc	120

caggatcaag	tggtggaagg	cttgcaaggt	ggcttcagcc	agattcatat	gcggatcctc	180
agaaaacatc	tttgatcctg	gaataaggat	gatattcggt	gtggttgccc	taccaccata	240
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ataactggat	taaattagca	gacatctata	tactggctgc	aatgactgat	aaaattttag	360
aaatgccaag	tgctgagrgt	ccatttggtc	tacctctttt	atataaagg	tgatgctgaa	420
agtttggtta	aatgacttgt	ttatattaat	tagtcccaa	gtgtccaagt	tacacctgtt	480
ttttttgtga	gtttgttctt	tacattttgc	tacctgttac	ggggactcaa	aggagggata	540
agaaagtatc	catctaaaga	gtgctagaca	catacagtga	agccctcaa	tatgtattga	600
ttgaataaat	gcatgaaaga	atacattttt	aaattttgtg	tatagttttg	aaagactcaa	660
gtacgttctg	tgtttggtat	tactgaaacc	acatttttaa	aataacactc	attaagttag	720
aaatatatga	gttttagattg	taaaagaatg	aggaattgaa	atagttgtat	accatattga	780
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atattataca	taattatttg	tgattttaatc	tgtaatatg	aatatctcat	ttaaaacttt	900
tattttctgaa	aaaattatat	tgaataaaat	tttatatagg	cagtccccag	ccctttcctc	960
cttcaaagtt	gtcttataga	gtgattgggt				990

<210> 25

<211> 1208

<212> DNA

<213> Homo sapiens

<400> 25

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aggtagacga	gctgttcgac	gtaaagaacg	ccttctacat	cggcagctac	cagcagtga	180
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tcggagggag	agcatcggtg	ccgagctgga	ccgagagatg	agcaggagck	tgacgtgac	420
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ccacctgcat	ccctctgggg	caggagccca	ccccagcac	ccccatctgt	taataaatat	1140
ctcaactcca	rggtgttcca	cctgaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1200
aaaaaaaa						1208

<210> 26

<211> 1922

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1022)

<223> n equals a,t,g, or c

<400> 26

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gcctcgatcc	ccggctcctt	caggctgtca	ccgatctggg	ctggtcgcga	cctacgctga	120
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cgggctccgg	gaagacggcc	gcttatgcta	ttccgatgct	gcagctgttg	ctccatagga	240
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aa						1922

<210> 27
 <211> 1951
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1892)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1930)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1934)
 <223> n equals a,t,g, or c

<400> 27						
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agtacacgct	ggtggtagat	gagcatgcac	agctggagct	ggtgagcctg	cgccgtgctt	180

cggagactac	agtgcagaga	gtgactctgc	caccgtctat	gacaactgtg	cctccgtctc	240
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tgctgcctc	tccgaggaa	tccacgcctg	atgaaccoga	cgtccatttc	tccaagaaat	360
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<210> 28

<211> 3989

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (17)

<223> n equals a,t,g, or c

<400> 28

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gaactatgat	ttggactcaa	gggtttgtag	atttcctcct	tcattctaata	ttcagtgctc	240
aaaattcctt	catccrtgaa	cgagctgggc	atttgatgag	acagggcyga	atactgcagt	300
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aaaaaaaaaa	aaaaagcgga	cgcgtgggc				3989

<210> 29

<211> 3735

<212> DNA

<213> Homo sapiens

<220>
 <221> SITE
 <222> (110)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (3690)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (3716)
 <223> n equals a,t,g, or c

<400> 29

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ggttgaagga	actgatgtaa	cagggattga	agaagtagta	attccaaaaa	agaaaacttg	180
ggataaagta	gccgttcttc	aggcacttgc	atccacagta	aacagggata	ccacagctgt	240
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<210> 30

<211> 1667

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1628)

<223> n equals a,t,g, or c

<400> 30

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 <222> (666)
 <223> n equals a,t,g, or c

<220>
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 <222> (682)
 <223> n equals a,t,g, or c

<220>
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 <222> (3181)
 <223> n equals a,t,g, or c

<220>
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 <222> (3184)
 <223> n equals a,t,g, or c

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 <211> 971
 <212> DNA
 <213> Homo sapiens

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 <222> (957)
 <223> n equals a,t,g, or c

<220>
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 <222> (964)
 <223> n equals a,t,g, or c

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<210> 34
 <211> 1792
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1767)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1768)

<223> n equals a,t,g, or c

<400> 34

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<210> 35

<211> 896

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (870)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (877)

<223> n equals a,t,g, or c

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tctgcttttg	gtgtttgtac	atgttaagaa	ttgaccagtg	aagccatcct	atttgtttcc	480
ggggaacaat	gcgggggtgg	garaggggag	aggagagagt	ttgggaaagg	gagatggaga	540
agaactcaag	gacattgcaa	ccctgcccgg	cgcagatctg	attttcacat	ctctacctgg	600
acattgagcc	tcccaggcac	catgttgagg	agagatgaaa	accagggcgg	tagaacttca	660
gggtgaagga	cagagtcctg	ggtggggcag	cggctgcagg	gcgcaccaga	gaaccagcc	720
agaggggggtg	tgagtaccag	tggtgttgct	tccaccctgc	agcaggtggg	atgaggtctg	780
tgtgtgtgtg	tgaaccatca	ttttttgatc	atcatgacca	atgaaacatt	gaaaaaaaaa	840
aaaaaaactg	gagggggggc	cgtacccean	tcgccgnata	gtgatcgtaa	acaatc	896

<210> 36

<211> 912

<212> DNA

<213> Homo sapiens

<400> 36

tgcacccacg	cgtccgggtca	gccagtcgca	tccagccatg	acagccttct	gctccctgct	60
cctgcaagcg	cagagcctcc	taccaggac	catggcagcc	ccccaggaca	gcctcagacc	120
aggggagggg	gacgaagggg	tgcagctgct	acagacaaa	gactccatgg	ccaagggagc	180
taggcccggg	gccakccgcg	gcagggtcgt	ctggggctctg	gcctacacgc	tgctgcacaa	240
cccaaccctg	caggtcttcc	gcaagacggc	cctgttgggt	gccaatgggtg	cccagccctg	300
arggcaggga	akgtcaaccc	acctgcccct	ctgtgctgag	gcatgttcc	gcctaccatc	360
ctcctccctc	cccggctctc	ctcccagcat	cacaccagcc	atgcagccag	caggtcctcc	420
ggatcacagt	ggttkgggtg	aggtctgtct	gcactgggag	cctcargarg	gctctgctcc	480
accacttg	ctatgggaga	gccagcagg	gttctggaga	aaaaaactgg	tgggttaggg	540
ccttgggtcca	ggagccagtt	gagccagggc	agccacatcc	aggcgtctcc	ctaccctggc	600
tctgccatca	gccttgaagg	gcctcgatga	agccttctct	ggaaccactc	cagcccagct	660
ccacctcagc	cttggccttc	acgtgtgga	agcagccaag	gcacttcctc	accccytcag	720
cgccacggac	ctytytgggg	agtggccgga	aagctcccg	gcctytgccc	tgccaggccag	780
cccaagtcac	gactcagacc	aggtcccaca	ctgagctgcc	cacactcgag	agccagatat	840
ttttgtagtt	tttatkcctt	tggtatttat	gaaagaggtt	agtgtgttcc	ctgcaataaa	900
cttgttcctg	ag					912

<210> 37

<211> 1382

<212> DNA

<213> Homo sapiens

<220>
 <221> SITE
 <222> (787)
 <223> n equals a,t,g, or c

<400> 37
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 gagggcctag aagggaaga ctgtctagt ggacaatgtc atattataaa tttggaatgc 120
 tgaatagaaa attatagatt ttgatattga aggaaatgaa gcgaagcyta aatgaaaatt 180
 cagctcgaag tacagcaggc tgtttgccctg ttccgttggt caatcagaaa aagaggaaca 240
 gacagccatt aacttctaata ccacttaaag atgattcagg tatcagtacc cttctcgaca 300
 attatgattt tctctctcta cctacagatt gggcctggga agctgtgaat ccagagtktg 360
 ctctgtaat gaaaacagt gacaccgggc aaataccaca ttcagtttct cgtcctctga 420
 gaagtcaaga ttctgtcttt aactctattc aatcaaatac tggaagaagc cagggtggtt 480
 ggagctacag agatggtaac aaaaatacca gcttgaaaac ttggrataaa aatgatttta 540
 agcctcaatg taaacgaaca aacttagtgg caaatgatgg aaaaaattct tgtccaatga 600
 gttcggggagc tcaacaacaa aaacaattaa gaacacctga acctcctaac ttatctcgca 660
 acaaagaaac cgagctactc agacaaacac attcatcaaa aatatctggc tgcacaatga 720
 gagggctaga caaaaacagt gcactacaga cacttaagcc caattttcaa caaaatcaat 780
 ataaganaca aatgttggat gatattccag aagacaacac cctgaaggaa acctcattgt 840
 atcagttaca gtttaaggaa aaagctagtt ctttaagaat tatttctgca gttattgaaa 900
 gcatgaagta ttggcgtgaa catgcacaga aaactgtact tctttttgaa gtattagctg 960
 ttcttgattc agctgttaca cctggcccat attattcgaa gacttttctt atgagggatg 1020
 ggaaaaatac tctgccttgt gtcttttatg aaatcgatcg tgaacttccg agactgatta 1080
 gagggccagt tcatagatgt gttggcaact atgaccagaa aaagaacatt ttccaatgtg 1140
 tttctgtcag accggcgtct gtttctgagc aaaaaacttt ccaggcattt gtcaaaattg 1200
 cagatgttga gatgcagtat tatattaatg tgatgaatga aacttaagta gtgataaaaag 1260
 gaagtttagc ataaattata gcagttttct gttattgctt aatttaccat ctccatagtt 1320
 ttatagctac tattgtattt cacttggtga attaaagtat ttgaattctt ttaaaaaaaa 1380
 aa 1382

<210> 38
 <211> 872
 <212> DNA
 <213> Homo sapiens

<400> 38
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 atcccggctg gccatgctgt tagacccttt catccttctc ttctgcctct tctcaacagc 120
 tgcccagctc tgtttgaat tcatatacat acagttctaa tactgatgta tttaccctca 180
 taagccactc aaccagaat cttatttgaa ttataatcca gaaacatcag gtgacgtgtg 240
 agactactgt atgagaaaga gacagtttaa gggtcagtcc aatggaaaaa agagtctctca 300
 gagctttctt tagcttattc tcatcaaaga gctttctctg cagaaggaaac ctactggttc 360
 ctcccttcca gtcctagaaa tctgacctc gagtggctta atcctgctag cacctctctc 420
 tcgcactctg gtgccaaatg actccaggaa ctgggccatg atgtgggtggg aatgacctta 480
 cctgagcat cctactcatg cattgaacaa cagctaagag cagagcttag agcttagagc 540
 tggggcctgt aagggtgagag gaatcacatc ctgcagaagt ctgtcctgag aagcaggtac 600
 tcctgtcaca gcagagacac agtggatacc tgagtaacaa taatacaaga caggacgtgg 660
 gmacagcaaa agatttgggt gtcagaagar gccgagaaca cttycaggca ggaacattca 720
 rarttgttct tggaggaart aggcmcsaag gctgggcagg atttcmcggg gcagagatgg 780
 agcaagcaat tgaaatgaaa gccatggcat gggaaaagga gcactggcca caggagatgc 840
 aacgttgtga tgcaaggcca ctgtggagcc at 872

<210> 39
 <211> 812

<212> DNA
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (794)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (806)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (810)
 <223> n equals a,t,g, or c

<400> 39
 ggcagaggct caccacagca gagattgagg gggaaaccgtg atgaaatatt taagtattct 60
 gcttgatgat aataattttt ctcttatgtt aatgttggt ccgtttgggt gtttagcttt 120
 tgaaaggagt atgaaaatgc ggaatggggc tttggggctt gaggagggtg gatctctagt 180
 gtttaaaaaa ttttaattgca caaatagaaa taattcacc acattattga accccactaa 240
 agcatatcct ttttgtccat attcctttcc tgctgccctc gtgtgtacca ttattactca 300
 gttgtgattt gagctcgttc cacttaaagt cattcataga tacttttgcg tcgtgttkga 360
 atatttattg aatttctatt ctgtgtttta cttaattact ttattatgga acctttacac 420
 aggtctggtg tacttgttct ttgaaaagtc ttatgttgac caccatcact gagcatatag 480
 ctttttcctt atttccttgg gataattacc cgaagtggaa ataccgaatc aaacttctgt 540
 tttctttctt tggcactatt atataaattg tttccaaac aaggcatgtt tacaatagac 600
 atttttcaaa atctgggtat ttgtcctatt ttgtctctcg tatgcagaat tcagcggggt 660
 gccaaagtcg tttctgtgtg gggtgagaga caggctgtgc agcccactgt tgcataggac 720
 taactactac aaatcatgct gagaccgagc tatttttgcg gcttagargc tttgcagcct 780
 tgagtaagtt tcgncatctg gaaacnttgn aa 812

<210> 40
 <211> 1515
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (69)
 <223> n equals a,t,g, or c

<400> 40
 aattcggcac gagggaaatt caagcacttt tcttaaaaga agggggaatg gatgctgaaa 60
 caacacgtnt cccacaaagg gagcagacac tgggcttggt aagctgcccc ataccttccc 120
 cacagaactg ggggtccggc tccctgacat gcagatttcc acccagaaga cagagaagga 180
 gccagtgtc atggaatggg ctgggggtcaa agactgggtg cctgggagct gaggcagcca 240
 ccgtttcagc ctggccagcc ctctggaccc cgagggttga ccctactgtg acacacctac 300
 catgcggaca ctcttcaacc tcctctggct tgccctggcc tgcagccctg ttcacactac 360
 cctgtcaaag tcagatgcca aaaaagccgc ctcaaagacg ctgctggaga agagtcaagt 420
 ttcagataag ccggtgcaag accggggttt ggtggtgacg gacctcaaag ctgagagtgt 480
 ggttcttgag catcgcagct actgctcggc aaaggcccgg gacagacact ttgctgggga 540
 tgtaactggc tatgtcactc catggaacag ccattggctac gatgtcacca aggtctttgg 600
 gagcaagttc acacagatct caccctctcg gctgcagctg aagagacgtg gccgtgagat 660
 gtttgagggtc acgggcctcc acgacgtgga ccaagggtgg atgcgagctg tcaggaagca 720

tgccaagggc	ctgcacatag	tgccctcggt	cctgtttgag	gactggactt	acgatgattt	780
ccggaacgtc	ttagacagtg	aggatgagat	agaggagctg	agcaagaccg	tggtccaggt	840
ggcaaagaac	cagcatttcg	atggcttcgt	ggtggagggtc	tggaaccagc	tgctaagcca	900
gaagcgcgtg	accgaccagc	tgggcatggt	cacgcacaag	gagtttgagc	agctggcccc	960
cgtgctggat	ggtttcagcc	tcatgaccta	cgactactct	acagcgcatac	agcctggccc	1020
taatgcaccc	ctgtcctggg	ttcgagcctg	cgctccagggtc	ctggaccgga	agtccaagtg	1080
gcgaagcaaa	atcctcctgg	ggctcaactt	ctatgggtatg	gactacgcga	cctccaagga	1140
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cctgctctag	gtgggcattg	cggcctccgc	ggtggacgtg	ttcttttcta	agccatggag	1440
tgagtgagca	ggtgtgaaat	acaggccttc	actccgttaa	aaaaaaaaaa	aaaaaaaaaa	1500
aaaaaaaaaa	aaaaa					1515

<210> 41

<211> 704

<212> DNA

<213> Homo sapiens

<400> 41

aagatggttg	cgcccagagc	ttcgctctat	gctgctcccc	tgagagaggc	gtttccatca	60
accagttttg	caaggagtgc	aatgagagga	caaaggacat	caaggaaggc	attcctctgc	120
ctaccaagat	tttagtgaag	cctgacagga	catttgaaat	taagattgga	cagcccactg	180
tttcctactt	cctgaaggca	gcagctggga	ttgaaaaggg	ggcccggcaa	acaggggaaag	240
aggtggcagg	cctggtgacc	ttgaagcatg	tgtatgagat	tgcccgcatac	aaagctcagg	300
atgaggcatt	tgccctgcag	gatgtacccc	tgctgctctgt	tgtccgctcc	atcatcgggg	360
ctgcccgttc	tctgggcatt	cgcggtggtga	aggacctcag	ttcagaagag	cttgacagctt	420
tccagaagga	acgagccatc	ttcctggctg	ctcagaagga	ggcagatttg	gctgcccgaag	480
aagaagctgc	caagaagtga	cccttgcccc	accaactccc	agatttcaaa	ggaggtagtt	540
gcaaaagctg	tgcccgaagg	gaggaaggag	gtcacaccaa	tatgatgatg	gttttcatga	600
ctttgaatga	tatatTTTTg	tacatctagc	tgtatcgagg	catcaggcct	gaataaacat	660
cctttcttaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaa		704

<210> 42

<211> 1094

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (196)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (226)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (302)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (596)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (952)

<223> n equals a,t,g, or c

<400> 42

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cagtcccact	attccacaca	tactgttact	gtttctttat	cctactttct	caattttgga	120
acatagttgc	agttactgca	ttgaatacct	gtgggtttgc	ctgttgctct	gtctgtctct	180
gtgggtcttg	taatantgga	ttccagagat	aaaatggaca	gttgtnatgc	acagttaatt	240
cagaaactag	accttacttg	ctgtgtgaaa	taccaactaa	attctcagtg	aactcagctg	300
anctttatct	ccttttggtt	cccccaattt	taatttcagt	tcaggcccag	aaagatggaa	360
tcccagctaa	gaaatacaag	ttacaccctg	tactagcagc	ccatgtgtgc	atgttcttta	420
agtgtctctg	cagctatgtc	atcttatattg	atctccctgt	attattataa	gcaaagcaaa	480
tttgaggaaa	aaaacccata	ataccacacc	tcatTTTTTT	caagtaatat	ggtcataagt	540
ctcatyctyc	atataatatg	ttgagtatgc	agtatattat	gtgttaggct	ctgganaggc	600
agaggttaga	tcatgtwaca	gatcatatck	gattaggcag	ataaacagta	ttttaacctt	660
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tggcaagggtg	gctcacacct	gtaatcccag	cactttggga	ggctgagggtg	gggtggatcac	900
ctgaagtcag	gagttcgaga	ccagcctgac	caacatggcg	aaaccctgtt	tntactaaag	960
acacacwwaa	aattrgcccag	tgggtgggtgc	atgtgcttgt	agtcccactt	agctactcga	1020
gaggctgagg	caggagaatc	gcttgaaccc	gggaggcaga	ggttgcagtg	aggcaagatg	1080
gcacctctac	actc					1094

<210> 43

<211> 1821

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1801)

<223> n equals a,t,g, or c

<400> 43

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cctgtgggtgc	tgtggagatg	tgtgtagtgg	tcttagctct	ttgttgagct	tgtgtgtgtg	120
ttgtgtagtc	ttagctgtat	gctgaaattg	ggcgtgtgtt	ggagggcttc	ttagctcttt	180
ggtgagattg	tatttctatg	tgttgtatc	asctgaatgt	tgtctggaaat	aaaaccttgg	240
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gctcctttgt	acaacaggaa	aatgcctcaa	agccttgctt	cccagcaacc	tggggctggt	360
tcccagtgcc	tggctcctgc	ccttcctggt	tcttatctca	aggcagagct	tctgaatttc	420
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tggctgtcat	tgctttcttc	ctccccattt	ggacccttct	ctgcccttac	atTTTTgttt	840
ctccatctac	caccatccac	cagtctattt	attaacttag	caagaggaca	agtaaagggc	900
cctcttggct	tgattttgct	tctttctttc	tgtggaggat	atactaaagt	cgactttgcc	960
ctatcctatt	tggaaatccc	taacagaatt	gagttttcta	ttaaggatcc	aaaaagaaaa	1020

acaaaatgct	aatgaagcca	tcagtcaagg	gtcacatgcc	aataaacaat	aaattttcca	1080
gaagaaatga	aatccaacta	gacaaataaa	gtagagctta	tgaaatggtt	cagtaaggat	1140
gagtttggtg	ttttttgttt	tgttttgttt	tgktttttta	aagacggagt	ctcgcctctgt	1200
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ggaaaacacc	ttgtctgcat	tcacttttaa	atgtcaaaac	taatttttat	aataaatgtt	1740
tattttcaca	ttgaaaaaaa	aaaaaaattt	aaaaacycgg	ggggggcccs	gwacccatt	1800
ngcccctaag	gggggggggtt	t				1821

<210> 44

<211> 1024

<212> DNA

<213> Homo sapiens

<400> 44

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ggcaagaact	gcaccgcagg	gccgtctaca	cctaccacga	gaagaagaag	gacacagcgg	120
cctcgggcta	tgggacccag	aacattcgac	tgagccggga	tgccgtgaag	gacttcgact	180
gctgttgctc	ctccctgcag	ccttgccacg	atcctgttgt	cacccagat	ggctacctgt	240
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ggcccagtg	gggtcctcca	agtaaggaca	aggacaaagt	gctgcccagc	ttctggatcc	540
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gagacaaact	cacagaccgc	gacatcatcg	tgctgcagcg	gggcgggtacc	gsttcgcggg	900
ctccggagtg	aagctgcaag	cggagaaatc	acggccgggtg	atgcaggcct	gagtggtgtc	960
gggagaccaa	ataaacccggc	ttgggtgcgc	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1020
aaaa						1024

<210> 45

<211> 983

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (976)

<223> n equals a,t,g, or c

<400> 45

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gccccctggga	acaagccgga	gctgtatgag	gaagtgaagt	tgtacaagaa	cgccccggag	180
agggagaagt	acgacaacat	ggcagagctg	tttgcgggtg	tgaagacaat	gcaagccctg	240
gagaaggcct	acatcaagga	ctgtgtctcc	cccagcgagt	acactgcagc	ctgctcccgg	300

ctcctgggtcc	aatacaaaagc	tgccttcagg	caggtccagg	gctcagaaat	cagctctatt	360
gacgaattct	gccgcaagtt	ccgcctggac	tgcccgtgg	ccatggagcg	gatcaaggag	420
gaccggccca	tcacatcaa	ggacgacaag	ggcaacctca	accgctgcat	cgagacgtg	480
gtctcgctct	tcatcacggg	catggacaag	ctgcccgtgg	agatccgccc	catggatgag	540
atccagcccg	acctgcgaga	gctgatggag	accatgcacc	gcatgagcca	cctcccaccc	600
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caactcactg	tctgcagctg	cctgtctggg	gtctgtcttt	ggtgtcagaa	cttttggggc	900
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kgsggccggg	cccantccc	ccc				983

<210> 46

<211> 2421

<212> DNA

<213> Homo sapiens

<400> 46

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cgctgggggag	ccagcacagc	caccacacag	aagaaacctt	ccatcagtat	caccactgaa	420
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<210> 47

<211> 840

<212> DNA

<213> Homo sapiens

<400> 47

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<210> 48

<211> 2432

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (593)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2049)

<223> n equals a,t,g, or c

<400> 48

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cggtcataca	accaggagca	ctcccagagc	ttcacgtttg	atgatgcca	acaggaggac	180
cggaaagagac	tgccggastg	ctgggtctccg	tcctggaaca	gggcttgcca	ccctcccacc	240
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tcaccagccg	ccagagcctg	caggcaytag	cctgytatgy	tgacatctct	gtctctgagg	360
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ggacaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aa			2432

<210> 49

<211> 1742

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (570)

<223> n equals a,t,g, or c

<400> 49

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cg						1742

<210> 50

<211> 1487

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1486)

<223> n equals a,t,g, or c

<400> 50

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<210> 51

<211> 1328

<212> DNA

<213> Homo sapiens

<400> 51

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<210> 52

<211> 1856

<212> DNA

<213> Homo sapiens

<400> 52

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ggggtaaagt	tttacttcaa	aatgactcca	tatttcaaat	atctgttttag	actgtgaagg	1740
ccaaataatt	tttaagaaaa	catttgaaga	gtagtgtgtt	tgcatthgtg	aataatctta	1800
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<210> 53

<211> 1558

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (17)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1514)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1551)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1556)

<223> n equals a,t,g, or c

<400> 53

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gcaattgtga	gttgtgtgc	tccagatata	atctttaact	cctttgcctt	ctccacatac	240
atttccaagt	cctgttcatt	ctacctccaa	aatgtatctt	gtatccatto	atctctctcc	300
atcttcaatc	tatttcaatg	ccccatcatc	tcttgcatgg	aggagtgtaa	taattggcta	360
actggcctgt	tcttacattt	taaaatcaaa	agatgtgaca	ggtgaaatgc	ctatttcagt	420
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agcagtgtga	aaaagactgc	ttggcccttt	acagggaaaag	caggtccact	gtggcctgtg	540
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cctgttaa	ttgtaaacaa	tctaattaaa	tggcatcagc	actttaacca	aaaaaaaaaa	1500
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<210> 54

<211> 948

<212> DNA

<213> Homo sapiens

<400> 54

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ccaggctctt	tctgcagwca	taccgcggac	ccaatgggcg	ccctgcacac	ccgtttctgg	180
ggccgctcaga	cttgataca	tcgtaaactc	cgctccacg	gaacgtctcg	cctkgcgagc	240
aagmtcggaa	tccagttcct	caggaacccc	tccaaaaccc	acacccccag	ggacgcccgt	300
ttccgggatc	ccggscaaac	gccggaccct	cagtcgctcc	aggccccctc	accctcaaag	360
tgtagcgcgc	ccaaccgagc	aacctcggtt	tggtccctaa	aaccccgcc	cctctataag	420
caccgcccc	gctctgacaa	aaccccgcc	ccaggctcggc	aggctccgct	tcttttcttc	480
tccgcggggg	gattcagtc	agtgattggg	tttgtggctc	caggcctcgc	ccacagacgg	540
acagaccct	ccctttcttc	cggcaaaagg	accgagccct	ggggtagtaa	ggscaccaca	600
ctcctgtttt	ttgcaagtac	atttttgtcc	ytccctccac	caggatatctg	cctattttct	660
tgctaattccc	agaacctttc	cttttgcttt	ttttaaggac	atttggaag	ttcctgggtgt	720
aggacccttc	tccctgggat	aagaaacctg	cctgtaaacg	ctctgtaa	actcccttc	780
acccatccca	gcccctgggc	agccgggcag	aaggggaatcc	aggctatgga	cctcccaagt	840
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<210> 55

<211> 990

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (751)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (879)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (888)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (897)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (899)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (901)

<223> n equals a,t,g, or c

<400> 55

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agcccctcag	ccatgttggg	agccaagcca	cactggctac	caggtccctc	acacagtccc	240
gggctgccct	tggttctggt	gcttctggcc	ctggggggccg	ggtggggcca	ggaggggtca	300
gagcccgtcc	tgctggaggg	ggagtgcctg	gtggtctgtg	agcctggccg	agctgctgca	360
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gtccgaagcc	accaccatga	gccagcaggg	gaaaccggca	atggcaccag	tggggccatc	480
tacttcgacc	aggtcctggt	gaacgagggc	ggtggctttg	accgggcctc	tggctccttc	540
gtagcccctg	tccgggggtg	ctacagcttc	cggttccatg	tgggtgaagg	gtacaaccgc	600
caaactgtcc	aggtgagcct	gatgctgaac	acgtggcctg	tcattctcagc	ctttgccaat	660
gaccttgacg	tgaccgggga	ggcagccacc	agctctgtgc	tactgccctt	ggaccctggg	720
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cagcccctga	caactttctt	ctgccctctc	ttgcccana	aacagcnaaa	gcagganana	900
nactccctct	ggctcctatc	ccacctcttt	gcatgggaac	ctgtgccaaa	caccaagtt	960
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<210> 56

<211> 1603

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (328)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (336)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (341)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (788)

<223> n equals a,t,g, or c

<400> 56

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ccgcgcctct	agccgctgct	gtcttcgtgg	gaggcgccgt	gagttcgccg	ctggtggctc	180
cggacaatgg	gagcagccgc	acattgcact	ccagaacaga	gacgaccccg	tcgccagca	240
acgatactgg	gaatggacac	ccagaatata	ttgcatacgc	gcttgccctt	gtgttcttta	300

tcattgggtct	ctttggcgctc	ctcattttngc	camctnngctt	naagaagaaa	ggctatcggtt	360
gtacaacaga	agcagagcaa	gatatcgaag	aagaaaaagg	ttgaaaagwt	agrattgaat	420
gacagtgtga	atgaaaacag	tgacactgtt	gggcaaatcg	tccactacat	catgaaaaat	480
gaagcgaatg	ctgatgtytt	aaaggcgatg	gtagcagata	acagcctgta	tgatcctgaa	540
agccccgtga	ccccagcac	accagggagc	ccgccagtga	gtcctgggct	ttgtcaccag	600
gggggacgcc	agggaaagcac	gtctgtggcc	atcatctgca	tacgggtgggc	ggtgtwgtcg	660
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agtccagaga	gagcagacca	cggcgccaag	gcgagggtcac	ggtcctttct	gttggcagat	780
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gtggcacaga	gtagcagggtg	agccgtgggt	ttgggtgacat	tgggggcaga	gtggtgcagg	960
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aactagaatt	cacatcaccc	accatatagg	gcttgcatta	ccacgaggca	gaaagcacct	1260
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acctcaatc	gaatatttct	cttcccacca	aatattttga	ggcaattgaa	aagccacagt	1560
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<210> 57
 <211> 1052
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (250)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1051)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1052)
 <223> n equals a,t,g, or c

<400> 57						
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cctccctacc	tttcccagac	ctctcactcc	tgccctgggtg	tccaacccgt	tctgtggcca	180
gagtatacat	tttggaaacct	cttcgaggcc	atcctgcagt	tccagatgaa	ccatagcgtg	240
cttcagcagn	aaggcccgag	acatgtatgc	agaggagcgg	aagaggcagc	agctggagag	300
ggaccaggct	acagtgacag	agcagctgct	gcgagagggg	ctccaagcca	gtggggacgc	360
ccagctccga	aggacacgct	tgacaaaact	ctcggccaga	cgggaagagc	gagtccaagg	420
cttcctgcag	gccttggaac	tcaagcgagc	tgactggctg	gcccgtctgg	gcactgcatc	480
agcctgaatg	aggctggcca	cctgccactt	tgccctgccc	tctgcctcca	gggctccmct	540
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cttggctggg	gagcccccca	ggccagggtt	gctggccata	gatacctttg	ggctgcctgr	660
gacaggctcc	tgaggaggat	tgagggtgaa	agtcctccac	gagtacacta	aacctaggtc	720
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atgcactttc	ttttccacc	agcacatcct	tcaacacaca	gaatttcagg	gaagagttct	840
ccccaaaacc	ctagctcttt	acccttccat	tttagccttc	caccagctt	ccacaaaaga	900
tttggtcta	ccttgatct	gctagtaaat	aactaatagg	caggcagta	tttgggtaag	960
gaaaaaaggg	gtgggagaga	cagaaaattt	gccactgct	gctcctccc	ttggstytcc	1020
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<210> 58
 <211> 814
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (6)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (32)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (751)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (770)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (784)
 <223> n equals a,t,g, or c

<400> 58	
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kgtttttttc	tttttcttct tctccttctc cttcttcttc tcttctcctt ctttcttctt 180
ttttttttca	gagtcttgct ctgtcaccaa gactggagtg aagtgatgtg atctcggctt 240
actgcaacct	gggaggcaga ggttgcatg agtcgagatg gtgccattgc tctcgtttgg 300
gcaacaagag	tgaaactctt gtctcaaaaa aaaaaaaaaa atgaggttta agacagtttt 360
gtcattactg	gtgggatctg gtcacacaag atagcattaa acgtgacatg gcacataaaa 420
ttgggttaaaa	aattttgttt tttaattacg taatgtaaaa gcccaacaaa cactttatgc 480
aagattggaa	tgtatcttca aattcagatt taataaacat gtaaagatcc tctgtatata 540
aaagttgtat	ttaatccctt gtgccccaa aatgctataa aagatcccaa gaatgttatc 600
tatgaaaaga	tagcaatagg gaatggtgaa caaataattt aatttgccaa ttctaaaaaa 660
catggactta	aaccccatga aaacttggtt ccatagtttt aactgtttta tggttccaat 720
acaaaaccag	agtggtttac attccacaat naccaaattt gcatccaatn ttggggtaat 780
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<210> 59
 <211> 1215
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (345)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1024)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1098)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1186)
 <223> n equals a,t,g, or c

<400> 59
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 gagtgcctctg ctacactcgt cccctcctg cctcatcttc cttctcagcc ttggttcctg 120
 atgggaacag aatggagggc ctgagaacat actttctaaa tgcctttgac ccaggaaccg 180
 attatctata tttgttccca ttttccttca cctgtgacatt ccagcattgt ctgactgtga 240
 ggtgggcctt tgagagcctc caggttcctc aaaacaggcc tgagcgatgg gcatcacacc 300
 ctctgcctac ccacrtgcct gcttacctgc cagataacca agtgnagatg tctgcgagtg 360
 gctagttttc acattcttac tagtgtttgg ytcacctttg ggcaaaggcc ccctctaggc 420
 cttgccccac ctccatcaaa cgcagacact gtagtcagac ctcagyaata taggaggcaa 480
 taatctttta acagtgtttt gcaaacaac aaaaagagaa aaatcccagc caggggaact 540
 cgccacctgc ccacgctagt tccatccacg ctcaagaccc gcccttagac caggcaggca 600
 aaggcccca tcacactcgg ccactagtgg ggtcctgagg ccaagaaaga aaccagacc 660
 tgtatgacaa gttgggktct ttccagaaca cgacagaaac agggggggcc ccttggtaat 720
 gccactccat actccagaag cattattcct tatttgggac agccaagggc agattcacag 780
 gttattgtag gaataaagac tagtttacia aggaraaaga gsccttgac ttcccmagga 840
 aaggtcaggt tagggctcct gtacccattc tgttccacca ctggttgatc tctctggcct 900
 ccaccagga atgccgtttc ctttttatgg atctgttggg aaccagagag aatcaacaga 960
 tcaatgacat aggatccgaa gtgcaatgat agtcacttct agtttggcat ttcacaaact 1020
 ctgnacagca aggtattggg aggttactca atttcaaaaag ggccccatgg ccaaatatgt 1080
 ttaggaaccg ctggttgnat ttcttttttt ggagacgcac tgtatataat atatgtcaaa 1140
 ggctttcgga attcctgcag gaaagaaatc agctttgtta aatccnaaaa aaaaaaaaaa 1200
 aaaaaaatag actcg 1215

<210> 60
 <211> 478
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (410)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (476)

<223> n equals a,t,g, or c

<400> 60

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cagtggagtc	ctgctggctg	taatcattaa	ttgtgaaatc	taaggagctt	agttcatggc	120
tctagaattt	cacagaaaar	tgygmtatga	tacgagcatt	aagtttattt	cttctgatct	180
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tgttacctct	aatgaattat	cctgattgta	agttaaaaat	caatatttcc	ccgtagtgag	360
gtttgctttt	taaaaagaak	kcttaaaaaa	aaaaaaaaaa	aaacgagttt	aagaaaagga	420
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<210> 61

<211> 618

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (548)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (560)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (562)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (584)

<223> n equals a,t,g, or c

<400> 61

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gctactaggt	aagccttctg	ggactttcag	atattttggg	gaagattgat	ttttgttctt	180
acatgctgtg	gacccttggc	catcaaatgg	tatggggaag	ctcatccgtc	tgtctgtgat	240

ggtcattgtca	gtcaggcgctc	tttttagtat	ttactgggtg	ctcagtactg	tgccagatgc	300
tgctcgggagc	cgtggtggta	tggaggagga	gtgctccaga	ggactctgct	gtgtggcagg	360
ccagcataaa	caagccaagg	ggaaaaggca	ggcatggaat	aaagggggag	aataccagt	420
tgtgacttac	tgctgactgt	gtggattagc	ctatcagcag	taatcaagca	gggcggaggg	480
cattatcttt	gagccagaag	agtgagcact	ggscggaggg	tggagcatca	agaggggggtg	540
taggaccnca	aggcttcttn	cnggggagac	aacgtcaata	agcngtcagt	agtcaccgac	600
agttttggga	agcaagg					618

<210> 62
 <211> 751
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (158)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (159)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (202)
 <223> n equals a,t,g, or c

<400> 62	
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tctgctgcta	cagctcatag aagtcaacaa ttttcttcaa cactggtagg cagcctctaa 120
atggccctga	tcacctcac ctctgccat tcacaccnnt gtaaaattcc acccctggac 180
ctagtgactc	acttctaaca angagaatac agcaaaagta acatcgcttc tgaggtgagg 240
ctacaaggag	actacgatgc ctgccttggt cacccttctc ctgctctttc cattgctccc 300
tctgatggaa	gccagttgcc atgtgatgag gtgccctatg gagaggccca cgtgacaagg 360
tattgtaaaa	agcctctgac caatagccat ctagaaacgg aggccagtc cagcagcctc 420
tgagatgaat	cctgcccaacc tgagcttgga gacagattct ctccctatcc tgccttgga 480
tgatcacagc	caccaccaac accttcactg cctggtgaga ggccaagcca gtgaacccaa 540
ggtaaaactg	acagaatcct gacccacaga aactgagata atgtttgtta ttttaagctg 600
ctcagtttgt	tacagagcaa tagataacta actcaaacac cataaaattc taatatttta 660
ttctatcaca	caaaccaggt aataccaagt aaatgccatt actatacaca tattttttgta 720
acacaattac	atgtgatttt ttaagaaggc t 751

<210> 63
 <211> 780
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (2)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (4)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (738)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (776)

<223> n equals a,t,g, or c

<400> 63

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ggcctgc	ggtgacttca	cattttccta	cctctccttc	taatctcttc	tagagcacct	120
gctatcccc	acttctagac	ctgctccaaa	ctagtgacta	ggatagaatt	tgatccccta	180
actcactgtc	tgcggtgctc	attgctgcta	acagcattgc	ctgtgctctc	ctctcagggg	240
cagcatgcta	acggggcgac	gtcctaatac	aactgggaga	agcctcagtg	gtggaattcc	300
aggcactgtg	actgtcaagc	tggcaagggc	caggattggg	ggaatggagc	tggggcttag	360
ctgggaggtg	gtctgaagca	gacagggaat	gggagaggag	gatgggaagt	agacagtggc	420
tggtatggct	ctgaggctcc	ctggggcctg	ctcaagctcc	tcctgctcct	tgctgttttc	480
tgatgatttg	ggggcttggg	agtccctttg	tcctcatctg	agactgaaat	gtggggatcc	540
aggatggcct	tccttcctct	taccttcctc	ccctcagcct	gcaacctcta	tcctggaacc	600
tgctctccct	ttctcccaa	ctatgcatct	gttgtctgct	cctctgcaaa	ggccagccag	660
cttgggagca	gcagagaaat	aaacagcatt	tctgatgcca	aaaaaaaaaa	aaaaaaaaacc	720
gcggccgaaa	gcttattncc	ctttaagtaa	gggggttaatt	tttagcttgg	gcactnggcc	780

<210> 64

<211> 588

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (565)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (566)

<223> n equals a,t,g, or c

<400> 64

ttccgaatta	atcgactcac	tataggaawt	gccgtcgcca	tgacccgcgg	taaccagcgt	60
gagctcgccc	gccagaagaa	tatgaaaaag	cagagcgact	cggttaaggg	aaagcgccga	120
gatgacgggc	tttctgctgc	cgcccgaag	cagagggact	cggagatcat	gcagcagaag	180
cagaaaaagg	caaacgagaa	gaaggaggaa	cccaagtagc	tttgtggctt	cgtgtccaac	240
cctcttgccc	ttcgctgtg	tgccctggagc	cagtccacc	acgctcgctg	ttcctcctgt	300
agtgtcacca	ggtcccagca	ccgatggcat	tccttttgcc	ctgagtctgc	agcgggtccc	360
ttttgtgctt	ccttcccctc	aggtagcctc	tctccccctg	ggccactccc	gggggtgagg	420
gggttacccc	ttcccagtg	tttttattcc	tgtggggctc	accccaaagt	attaaaagta	480
gctttgtaat	tccaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	540

aaaaaaaaaa aaaaaaaaaa aaaanncggg ggggggcccc cccccccc

588

<210> 65
 <211> 945
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (13)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (15)
 <223> n equals a,t,g, or c

<400> 65	naatacgatc atnanagggc gattgggtac gggccccccc tcgagttttt tttttttttt	60
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	cactgttaac ctttgggtgta taataaaaatc agacactttc ctttgcatta tgtcacatag	180
	aaatgtacaa ataaagtgtgta catatatata cacatatatg tatacactgt tttgcaactc	240
	gttatttttca ctttgcata tacaatgagc atttttccat gcaaatgaat gagacctctt	300
	attaaatgaa taagattggg tcaaaagatg agatgttgac aagagtcata tgtaaactctc	360
	agcaacatcg aatgactgga gtaaaacgat agcaaataat tatcaagaaa gtgcagacaa	420
	acagaaagca gtggcaacat taataacaga aaataattga attgtcagag aaattaatta	480
	aatgggataa ggacggtccc gagaatgcct atgggttagaa tgcagagccc taaatttctt	540
	tctyagaccc cttatctctt ccaaacacct ttccatctca tctccctccc ttgtcatttc	600
	ttcatcttta aaatgcctat agtctatgtc ctctttaaat tcttcgagag actgaagcag	660
	cctctgtcta aaattccctt ctgtttgctg gcgttcaaat tctccatacg ggcgtttttc	720
	ctccctcttt ggcacgctgc actttggcct tccttcgctt tctttgcagg gtttttgcag	780
	gatgttggtg ttgtttcctg cttaactctg tgcggggtag ttccctgctc cttttcttcc	840
	cccagatgtc tgtgaacaca gatcctggga cctcttcctt cccttggcca caagcacgca	900
	cggcacgctt gtctgcaggg cagtaaggag ctggtacctc gtgcc	945

<210> 66
 <211> 1866
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (262)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (674)
 <223> n equals a,t,g, or c

<400> 66

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acaagagcat	cttggatgta	ggacaatgga	agagttagat	gccttattgg	aggaactgga	120
acgctccacc	cttcaggaca	gtgatgaata	ttccaaccca	gctcctcttc	ccctggatca	180
gcattccaga	aaggagacta	accttgatga	gacttcggag	atcctttcta	ttcaggataa	240
cacaagtccc	ttgccggcgc	antcgtgtat	actaccaata	tccaggagct	caatgtctac	300
agtgaagccc	aagagccaaa	ggaatcacca	ccaccttcta	aaacgtcagc	agctgctcag	360
ttggatgagc	tcatggctca	cctgactgag	atgcaggcca	aggttgcagt	gagagcagat	420
gctggcaaga	agcacttacc	agacaagcag	gatcacaagg	cctccctgga	ctcaatgctt	480
gggggtctsg	agcaggaatt	gcaggacctt	ggcattgcca	cagtgcccaa	gggccattgt	540
gcacctgcc	agaaaccgat	tgctgggaag	gtgatccatg	ctctagggca	atcatggcat	600
cctgagcatt	ttgtctgtac	tcattgcaaa	gaagagattg	gctccagtcc	cttctttgag	660
cggagtggct	tggnctactg	ccccaacgac	taccaccaac	ttttttctcc	acgctgtgct	720
tactgcgctg	ctcccatcct	ggataaagt	ctgacagcaa	tgaaccagac	ctggcaccca	780
gagcacttct	tctgctctca	ctgcggagag	gtgtttggtg	cagaaggctt	tcatagagaag	840
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caatcactgc	tgtggaatca	tgataccact	tttagctctt	tgcatcttcc	ttcagtgtat	1740
ttttgttttt	caagagggaag	tagattttta	ctggacaact	ttgagtactg	acatcattga	1800
taaataaact	ggcttgtggg	ttcaataaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1860
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<210> 67

<211> 1152

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (668)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (745)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1015)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1088)

<223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1110)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1113)
 <223> n equals a,t,g, or c

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 caagcactgc atctgcttag tgaaggattt attgttcgga agatacattt tccccttkag 180
 cagagagtgg cgtatcctgg cagtcttcgg tgagccagtt gtaccaggat tatgaaatgc 240
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 tgcaactytt agttggcaga gaggaccact atggcgggta gctcttttct ttcctgccat 360
 tgtggggatg attccaggcc aaagatgatg garaagtatg gaaatcatct gaaagggtga 420
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 ccctgggagg gacggagggtg aatcctcctg agtacctgtg gttttcttac ttctgtctga 540
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 gcagatgcct tcaactttccc accraaaaaa ccccmaccaa acctaagacc ttactgcaac 660
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 ccctgagtg cgtgtgagaag gcmtnggctt tgccaggaaa tccagggaagg cagggccggg 780
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 aaaatagcag attggagcct tcgagaaggc agtaaattggc tgtttttatt gacaaaagga 960
 aacattttta ctgccatctc actgatggca tctcactgac ttaaaatgaa ggcangttgt 1020
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 ataggttggg tg 1152

<210> 68
 <211> 2483
 <212> DNA
 <213> Homo sapiens

<400> 68
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 cgccgccatg ggctcctcgc aaagcgtcga gatcccgggc gggggcaccg agggctacca 120
 cgttctgcgg gtacaagaaa attccccagg acacagagct ggtttgagc ctttctttga 180
 ttttattgtt tctattaatg gttcaagatt aaataaagac aatgacactc ttaaggatct 240
 gctgaaasca aacgttgaaa agcctgtaaa gatgcttatt tatagcagca aaacattgga 300
 actgcgagag acctcagtc caccaagtaa cctgtggggc ggccagggct tattgggagt 360
 gagcattcgt ttctgcagct ttgatggggc aaatgaaaat gtttggcatg tgcaggaggt 420
 ggaatcaaat tctcctgcag cactggcagg tcttagacca cacagtgatt atataattgg 480
 agcagataca gtcatgaatg agtctgaaga tctattcagc cttatcgaaa cacatgaagc 540
 aaaaccattg aaactgtatg tgtacaacac agacactgat aactgtcgag aagtgattat 600
 tacaccaaat tctgcatggg gtggagaagg cagcctagga tgtggcattg gatattggtta 660
 tttgcatcga atacctacac gccatttga ggaaggaaag aaaatttctc ttccaggaca 720
 aatggctggg acacctatta cactctttaa agatgggttt acagagggtc agctgtcctc 780
 agttaatccc ccgtctttgt caccaccagg aactacagga attgaacaga gtctgactgg 840
 actttctatt agtcaactc caccagctgt cagtgtgtt ctgactacag gtgtaccaac 900
 agtaccgtta ttgccaccac aagtaaacca gtcctcact tctgtgccac caatgaatcc 960
 agctactaca ttaccaggtc tgatgccttt accagcagga ctgcccaacc tcccacact 1020
 caacctcaac ctcccagcac cacacatcat gccaggggtt ggcttaccag aacttgtaaa 1080

cccagggtctg	ccacctcttc	cttccatgcc	tccccgaaac	ttacctggca	ttgcacctct	1140
ccccctgcca	tccgagttcc	tcccgtcatt	ccccttgggt	ccagagagct	cttctgcagc	1200
aagctcagga	gagctgctgt	cttccctccc	gccaccagc	aacgcaccct	ctgaccctgc	1260
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tgccaaggcc	cccaccaccg	ttgaggacag	agtcggcgac	tccaccccag	tcagcgagaa	1380
gcctgtttct	gcggctgtgg	atgccaatgc	ttctgagtca	ccttaacttt	gaaccattct	1440
ttggaattgg	cgtggtatat	ttaaccacgg	gagcgtgtct	ggaaacgcaa	actatcatta	1500
atttcatact	agtttgtacc	gtatctgtag	gcatacctgta	aataattcca	aggggaaaac	1560
taaacgagga	cgtgggttgt	atcctgccag	gttgagtggg	gctcacacgc	taggggtgaga	1620
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ctcacacgca	acatttcttg	tactttgtaa	gtcgtttgcg	agaatgcaga	ccacctcact	1860
aaactgtaaa	cggtaaagag	atTTTTtactt	ttgggtctccg	tgagtgcgat	ctctactaag	1920
gtttacacag	gaattccacc	tgaagacttg	tgttaaagtt	ctacagcgcg	cactgttaac	1980
tgaacgtctt	tttcttcagc	ctatacgcg	atccttggtt	tgagctctca	gaatcactca	2040
gacaacattt	tgtaactgct	gctgttgctt	tctacataca	ccttataaag	tgacatttca	2100
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cttggtttac	atctaaatta	caacccttaa	ttgccacgtg	tgacttact	actctccagt	2280
atgtcttatt	actctccagt	atgtcacgca	tctttaactt	ttcacgtcct	atgttttgct	2340
tctccatttt	ttaagagatg	gtaagttaac	tggaaattgat	ttactgaatg	aaattaaatg	2400
cagatatccc	tgtttttgaa	ataaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	2460
aaaaaaaaaa	aaaaaaaaaa	aaa				2483

<210> 69

<211> 536

<212> DNA

<213> Homo sapiens

<400> 69

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tataacctcc	gggttccttt	gcctcctttt	ccttagactc	cctccaaact	cgtgtatctt	180
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cataacatcc	tagttgaaaa	gtartttatc	aaccgcgttt	gaaaaatgaga	acagggttcac	300
agargctagg	ttacttgcca	aggtcgttca	attagtaacc	agtaacgcca	ggactgccag	360
tttcttgctt	ccgaattctc	atggtagctt	tcaccargct	ccccgtcmaa	tgctaacgtc	420
aactactgaa	ctagattagc	aaaaaggctt	tttaacagaa	ttcctgggtt	tcagagagag	480
tttctttcat	gaagcgcccc	atttctacag	aggaaaataa	actccaagca	gccagt	536

<210> 70

<211> 574

<212> DNA

<213> Homo sapiens

<400> 70

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agctcgcctt	tcttgccag	aggcgccgtt	tggactcacg	ggcggggcat	gatgggtgtg	120
ggtacgggca	cctcgctggc	gctctcctcc	ctcctgtccc	tgctgctctt	tgctgggatg	180
cagatgtaca	gccgtcagct	ggcctccacc	gagtggctca	ccatccaggg	cggcctgctt	240
ggttcgggtc	tcttcgtgtt	ctcgtcact	gccttcaata	atctggagaa	tcttgtcttt	300
ggcaaagat	tccaagcaaa	gatcttcctt	gagattctcc	tgtgcctcct	ggttgctctc	360
tttgcatctg	gcctcatcca	ccgagtctgt	gtcaccacct	gcttcattct	ctccatgggt	420
ggtctgtact	acatcaacaa	gatctcctcc	accctgtacc	aggcagcagc	tccagtcctc	480
acaccagcca	aggtcacagg	caagagcaag	aagagaaact	gacctgaat	gttcaataaa	540

gttgattctt tgtaaaaaaa aaaaaaaaaa aaaa

574

<210> 71

<211> 932

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (884)

<223> n equals a,t,g, or c

<400> 71

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agaacataag	gtcttggtgca	agaggagccc	tcgctcttct	gttccttctc	ggcaccacct	120
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tcagcaatgc	ttccagggg	atgttcattt	ttttattcct	gtgtgtttta	tctagaaaga	240
ttcaagaaga	atattacaga	ttgttcaaaa	atgtcccctg	ttgttttgga	tgtttaaggt	300
aaacatagag	aatggtggat	aattacaact	gcacaaaaat	aaaaattcca	agctgtggat	360
gaccaatgta	taaaaatgac	tcaccaaatt	atccaattat	taactactag	acaaaaagta	420
ttttaaatca	gtttttctgt	ttatgctata	ggaactgtag	ataataaggt	aaaattatgt	480
atcatataga	tatactatgt	ttttctatgt	gaaatagttc	tgtcaaaaat	agtattgcag	540
atatttgga	agtaattggt	ttctcaggag	tgatatcact	gcacccaagg	aaagattttc	600
tttctaacac	gagaagtata	tgaatgtcct	gaaggaaacc	actggcttga	tatttctgtg	660
actcgtgttg	cctttgaaac	tagtccccta	ccacctcggt	aatgagctcc	attacagaaa	720
gtggaacata	agagaatgaa	ggggcagaat	atcaaacagt	gaaaaggga	tgataagatg	780
tattttgaat	gaactgtttt	ttctgtagac	tagctgagaa	attgttgaca	taaaaataag	840
aattgaagaa	acacatttta	ccatttaaaa	aaaaaaaaaa	actngagggg	ggcccggtac	900
ccaaatcgcc	gcatagtgat	cgtaaacaaat	ct			932

<210> 72

<211> 996

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (584)

<223> n equals a,t,g, or c

<400> 72

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agatcaccgc	cgacttcaac	ctcctgcagg	tctcggagcc	ctcggagcca	tgtgtgagat	180
acctgcccag	gctgtacctg	gacatacaca	attactgtgt	gctggacaag	ctgccccgact	240
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ggaagctgta	caccatcatg	aactcgttct	gcaggagaga	tttggatttc	ctgttgatg	360
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aagggaactg	agaccagaga	aagaacccaa	gagaactaaa	gttatgtcag	ctaccagac	480
ttaatgggccc	agagccatga	ccctcacagg	tcttggtgta	gttgatctg	aaactgttat	540
gtatctctct	accttctgga	aaacagggct	ggtattccta	ccnnggaacc	tcctttgagc	600
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cctttttcta	acacagactt	tcttcactgt	ctttcattta	aaaagaaatt	aatgctctta	900

agatatatat tttaygtagt gctgacagga cccactcttt cattgaaagg tgatgaaaat 960
 caaataaaga atctcttcac atgaraaaaa aaaaaa 996

<210> 73
 <211> 785
 <212> DNA
 <213> Homo sapiens

<400> 73
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 cgragactga aatgggcctg ggtcttctcc tkgtcctgtg atwaaagtcc tctcttgaaa 180
 gtggagagca aaggcacaca gaggtgcgcg ctccacaagaa ttctctccgg tgactgggta 240
 atcaatgtta ctgctgtttc ctttgacagga aagaccacag caagattctt tcattcgtct 300
 cctcctagcc tgggggacca ggctcgaact gacctggac atcaaaggag ggattatgtg 360
 gctgctaaaag ccacgcggccc acagccctgt tcacrtcttg gtgcttctct tccccagagg 420
 ctggtcccag ccaggcacac acaaaaggca gattctcgta aacscagcct ccctccctgg 480
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 gctcagcaca tggctggatg cggatatttc tataattcca gaaagtcaca cagtcctct 660
 gtatgagacc agtggggcgcc atttaaaaga acaggatgag aatctaagat atattattaa 720
 taaatgtaat ggattttttt tttgtaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780
 aaaaaa 785

<210> 74
 <211> 1069
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (20)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (92)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (886)
 <223> n equals a,t,g, or c

<400> 74
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 gttcttaggc tcctgcacat gaagggtgtg gcctgtgggtg tgtgggctgc tctaggagca 180
 gatacaggct ggtatagagg atgcagaaag gtagggcagt atgtttaagt ccagacttgg 240
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 aggagggcag aagcttccat ttttgtcctt cctaagaccc tgttatttgt gttatttcct 360
 gcctttccga gtcctgcagt gggctgccct gtaccctgaa cctcatgagc ctctaaggga 420
 aaggaggpac aattaggacg tggcaatgag acctggcagg gcagartaca agcccagcac 480
 cagtgtccca gccttactgg gtccttacct tgggccaac aggaggggct gatacctcct 540
 tgctcttcct agatgcccac ctctacaat ctccagccac aagtcctctc caccctaggg 600
 ggcttgctgc atggcaataa ctcataatct gatttggagg tttgcccttt acaggggcag 660

attttctgct	cagttcaaca	atgaaatgaa	gaggaactcc	ctctttctac	agctcacttc	720
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tgtgtgccta	ctgaacctgg	caaataaaca	tcaccctgca	aagccaaaaa	aaaaaaaaaa	1020
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa		1069

<210> 75
 <211> 831
 <212> DNA
 <213> Homo sapiens

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gagcttttag	ctgtctctgt	ttcagttcat	tttacaggag	gtgaacatca	cacttccaga	180
aaactctgtc	tggtatgaaa	ggtataaatt	tgatattcct	gtctttcact	tgaatggcca	240
gtttctgatg	atgcatcgag	taaacacctc	aaaacttgaa	aaacagctcc	tgaaacttga	300
gcagcaaagt	actggargct	gactgatgcc	ctcatgattt	tcaccctctc	cttcccataa	360
agcatcttcc	taaggaaaatg	amcatggcct	gatactcatt	ttgtcacttg	tacagagccc	420
taaggatgtt	ctgaattcag	tggtgccaaa	taaatgttga	cattcccctt	ttggttgatg	480
gaagtatcag	tgtgggaact	gtttgcttaa	tggcatttta	taaaataaka	akakcatatt	540
agcagggagg	gagatgatgg	agggaggagg	aagtccattt	gtcttattta	tcctttttgt	600
attaatagag	aagcacttca	cagtcactgg	caatgccatt	tataggaaga	aggttctgca	660
ttcctgctgc	tcccgagggg	cttaactttt	taatgaaaga	ataaatgctc	ttccactcag	720
tagataaagt	gaaatgtgaa	ttgttaataa	ctgtgcacgg	tcaataaagc	gatgttttaa	780
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<210> 76
 <211> 590
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (12)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (27)
 <223> n equals a,t,g, or c

<220>
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 <222> (30)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (35)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (76)

<223> n equals a,t,g, or c

<400> 76

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tggtaccccc	ggctgcagga	ttcggcacga	gctgccaggt	gaggagcaga	gagactgttc	180
ccttggggtg	agaggtgtgg	gcatgagagc	caccatttgc	caagcagcaa	gaatgttcgt	240
gcttttttcc	cttccaaaat	atgcagggct	caggetccca	attccggggc	tgtctgcttt	300
gcttgtgttt	ctcctgtccc	tgttctcccg	gagggccag	gtggaactca	cgacagggag	360
ggagacgctt	cccaaaaacc	tgcagggcta	tttcccagaa	tttggttttc	aagtacaaaa	420
ctttttgtcc	tgtaagatat	atgcagcctc	acagaagcag	cctctgcctc	cactttacca	480
gctacgtttt	tatcttaagc	acatggggct	cccttagaac	ttactccact	gatttaaaaa	540
aaaaaaaaaa	aaactcgagg	ggggggcccg	tacccattcg	ccctaaaagt		590

<210> 77

<211> 1274

<212> DNA

<213> Homo sapiens

<400> 77

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ctctgaaaaat	cctatttggt	cctttatttt	atttgagttt	agagttccct	tctgggtttg	180
tattatgtct	ggcaaatgac	ctgggttatt	acttttcctc	cagggttaga	tcatagatct	240
tggaaactcc	ttagagagca	ttttgtctct	accaaggatc	agatactgga	gccccacata	300
atagatttca	tttactctta	gcctacatag	agctttctgt	tgctgtctct	tgccatgcac	360
ttgtgcggtg	attacacact	tgacagtacc	aggagacaaa	tgacttacag	atcccccgac	420
atgcctcttc	cccttggcaa	gctcagttgc	cctgatagta	gcatgtttct	gtttctgatg	480
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ctcctacaat	attcagtaca	tgaccactgt	catcctagaa	ggcttctgaa	aagaggggca	660
agagccactc	tgcgccacaa	aggttggggt	ccatcttctc	tccgaggttg	tgaaagtttt	720
caaattgtac	taataggstg	ggggccctgac	ttggctgttg	gctttgggag	gggtaagctg	780
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tgttaaaaaa	aaaa					1274

<210> 78

<211> 1133

<212> DNA

<213> Homo sapiens

<400> 78

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ttattttctc	tctcaaataa	cgtttctttc	aaaaacttct	ggctgaagta	taacatgctg	180
gtagttaaca	taaatcttgt	ctttctcttg	ttctttatct	ttctttgtta	tttagatgct	240
tgtataaatg	tctttttgtt	ttattaagtg	cctaattgac	agagcttaat	ttgaagaagt	300
gccctaattt	attgaccact	taagaattgc	ctttattggg	gtattttatt	tgttcctgcg	360

tctttttgat	gttggtcagt	ctactcatcc	ctgtgagtat	gtgtggggga	cagctgatag	420
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agggagcaac	aaggacagtt	tcacatgctt	agactttctt	ggaagaaaca	gtgaggagga	540
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tccaacatgt	tttcacttta	tttgcccctc	cctacatttg	ggttaggttc	catttggtatt	660
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tatagaacta	gctatttttag	ttacatagta	atgtaactaa	tggagagatt	tatagagaat	780
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attaataaat	aggtatttta	tttactgtaa	aaagtcaaac	ttcattatgt	agataaatct	1020
tattcttttc	attctttccc	ctgtttacat	cctttttaca	aagcttagtc	accaattaaa	1080
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<210> 79

<211> 661

<212> DNA

<213> Homo sapiens

<400> 79

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tggtgacgg	gatgcctgtc	ttgcctggac	gcaccactgc	tctcctgtcc	ctcaccttgg	240
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cccagactgg	ggattttgcc	aggggggcga	tgggaggagc	agggtgctttg	cctggcggt	480
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a						661

<210> 80

<211> 1378

<212> DNA

<213> Homo sapiens

<400> 80

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ggtgtcccag	gaagtcagcc	attactcccc	agtggaaatgg	atccaactcg	acaacaagga	180
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<210> 81

<211> 1440

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (38)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (41)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1128)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1129)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1440)

<223> n equals a,t,g, or c

<400> 81

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51

gtttctagtt	acagacacaa	tcatactgtg	atttttat	taatatggat	atgctatcaa	1200
actgtgatac	acttataatt	cactggtcct	gcatcaggag	atggagtggg	gaaaactgta	1260
tttaatacag	tttgtatctg	aataatctgt	atgggtttata	cagtttgtgt	tgttcagaga	1320
tgtttaaagt	ttgatctttg	tttttctaaa	gattaaaaaa	gcacttgccc	cactgtaaat	1380
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<210> 82

<211> 1381

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1379)

<223> n equals a,t,g, or c

<400> 82

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<210> 83

<211> 1706

<212> DNA

<213> Homo sapiens

<400> 83

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ccaactatca	tctgaggggt	aaagatgaga	agtagatcac	ttaataagac	aaaagcctgt	180
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gaaggccacc	attctgtccc	tcaaaactcg	cagctgcttc	tggtggcaca	gtggcttgaa	420
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cctggggaag	catctgattt	agaaatgtgg	gttagtgtcc	agagaatgga	aaaatagaca	540
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taggagaggg	agagacagat	agccagaaac	acaccagtga	agaggagaga	aaatgagtaa	660
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gcaggaacag	ctccagggtg	tgagaagaaa	aggcagaaga	tggtgtgctg	tggggatggg	1620
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<210> 84

<211> 573

<212> DNA

<213> Homo sapiens

<400> 84

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acttctctgtc	tactctttga	ttttgtttta	tttttagaaa	tgttttattt	tgttttattc	180
atctattcat	cttcagagac	atggctctggc	tctgttgccc	aggatggagt	gcattggtgtg	240
atcataggcc	actgcagtgt	tgagctcccg	ggctcaggcg	atcctcctgc	ctcagctycc	300
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gatgtcycaa	actagaagg	ctattaattt	aaaaaattaa	ggatagcatg	ccataattaa	420
aaataataac	agtgggaaaa	ggcaccttcc	aattgattcag	acatcaactt	gtgattttaa	480
aaaacgaaaa	ataaataata	ggaaaaaaag	gggaaaaagt	taaataaaaa	taaaatttaa	540
aaaaaaaaaa	aaaaactcga	ggggggcccg	gta			573

<210> 85

<211> 684

<212> DNA

<213> Homo sapiens

<400> 85

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caggcctccc	aggctgctct	ycacgtccct	tatgccacta	tcaacaccag	ctgcygccca	180
gctactttgg	acacagctca	ccccatggg	gggcgcctct	ggtgggcgtc	actccccacc	240
cacgctgcac	accggcccca	gggcctctgc	gcctgggcct	ccacacccat	ccctgcacgt	300
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actggtcccc	gcctcactct	tttccctgac	cctcgggggc	ccagggccat	ggaaggaccc	420
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ggtgtcatcc	ccttacttta	attcttgggc	ctccaataag	tgtcccatag	gtgtctggcc	540
aggcccacct	gctgcggtatg	tggtctgtgt	gcgtgtgtgg	gcacaggtgt	gagtgtgtga	600
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684

<210> 86

<211> 1036

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1020)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1024)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1032)

<223> n equals a,t,g, or c

<400> 86

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acaagccaga	ggagcccga	tgtgaggccc	cagatcacct	ccagggactt	ggggttccca	180
tctgaaatcc	tttatttttg	taccatgggg	tgggcccccg	gctgagaagg	aagaagcacc	240
ctctccccgg	cctcctctgt	ctgcacccgt	ggggctgtga	cttactcctg	cctccagggg	300
cggggcgggg	ccccctggga	cctcttaagg	cccaagggtg	gccccaggac	ctytgggcag	360
agtggaytgc	tcatggcaga	tgtgtggcaa	tgtctggctg	wgtctttccg	gcamctgcgt	420
yccctytccc	gggytcccct	gctgcatggt	ggatgtgctc	cttctctggc	cggtcacatt	480
gcctccttga	gccttagtcc	aggggggtcac	tyctcccacc	ccacctacct	cacagggttg	540
ttgtgagggt	gcacagagga	gcaaagtccc	tgaaggccct	caggcagtat	ataggggccg	600
cccaccttca	gctgccctgg	gatgggaagg	accagcccg	acccctgggc	ataacactgt	660
gtttgcaa	at	ggagattcag	gtattgggga	tgcaggttgt	ggggagctgg	720
taggggtagt	tggcttggcc	ttctctttgg	tgatcccacc	cccagccatt	tgcattgctg	780
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gtttgacttc	ccgggatggg	tccttgcttc	tcagctgtgt	ccgacccac	catgtaataa	960
aacccaaagg	aacagcaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1020
ccnngggggg	gnccccg					1036

<210> 87

<211> 908

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (805)

<223> n equals a,t,g, or c

<400> 87

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tgaatattat	tccattatat	ggatttacca	caattcattt	acctattcat	cttttgtttc	180

tgctgtctgg	ctattgtgaa	taatgcttcg	ataaacattc	atatacaagt	ttctatgtgg	240
ctttatgttt	tcatttctct	tggctatcta	catgggagta	gaattctagg	tcataatata	300
attttatgtt	taacttctca	aagaattgcc	aaaagggttt	tcatagtggc	tgcatcattt	360
acattcccac	cggcaatgta	caaggatttc	tatttttcca	tatccttgca	cttaccaca	420
cttctttttk	gtwatwattt	tgttttttca	ttattgccac	cctagtggat	gtgaaatggc	480
atcttattgt	tttgatttgc	atttctctaa	tgacaaatga	tatcatactt	tttttatgtg	540
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acctgtaatc	mtagcacttt	gggaggccaa	ggcgggcaga	tcacttgagk	tcaggacttc	720
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gcgtggtggc	aggtgcatgt	aatcntatct	actcaggagg	ctgaggcagg	agaatcgctt	840
gaaccacagga	ggcggaggct	gcagtgcagc	aagatcacgc	cattgcactc	tagcctgggt	900
gacacaga						908

<210> 88

<211> 655

<212> DNA

<213> Homo sapiens

<400> 88

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ctctcttctc	agattagaaa	actgcctcat	tttctgtcca	ctggatgtgc	agtcccagct	180
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ttgtttgact	ttcaatttca	tgggaatttt	tctcagctaa	actctaaatg	gtgattargc	600
aaaaaaaaaa	aaaaaaaaacy	graggggggc	ccggtaccaa	ttcgccctat	aatga	655

<210> 89

<211> 1102

<212> DNA

<213> Homo sapiens

<400> 89

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cagaggggtg	ggacatatta	cgggcgcgga	tccctcttgg	agtgcagatga	ctctccggag	180
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cttttacttt	cctgtgaagg	ttttagtgcc	ttttaaaaaa	tgctatata	taagcttggt	420
aatacttcca	tgtgtgatatt	gtggccatca	gtttccccgg	gcacaggcct	gcacattttg	480
ccttcacacg	ctgggtggtt	tttcattttc	acttctattt	ctcgttcttc	tatcgtttta	540
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ctctctactt	tctacagtga	attctctgay	gtgtctggga	gtwtgggggt	ctgggtaaga	660
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tgcaggtggg	ccgatgaagct	caggggtggg	accagtatct	cacagttctc	tttgcattggc	1020
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gaacaaaatt aaaccagcca gg

1102

<210> 90
 <211> 1533
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (12)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (123)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1522)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1527)
 <223> n equals a,t,g, or c

<400> 90							
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tgncctgggtgc	tgctgaaccc	gcgcggcgcc	aagggcaagg	ccttgcaagt	cttcggagt		180
cacgtgcagc	cccttttggc	tgaggctgaa	atctccttca	cgctgatgct	cactgagcgg		240
cgggaaccacg	cgcgggarct	ggtgcggctc	gaggagctgg	gccgctggga	cgctctggtg		300
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<210> 91

<211> 575

<212> DNA

<213> Homo sapiens

<400> 91

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gccagagctg	tacctggggc	cctttgagct	gaggtggaag	ccagagtctg	aagctcagca	180
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ctgcttggt	tctttctcta	ccacagarcc	aggctgcaaa	ttttacaaac	ttttacactc	420
tggttccctt	ttaaataata	atttcaatgt	taagtcactt	ccttgctccc	atatctgatt	480
taggttgctg	gaagtagcca	agtcacctct	tgaatgcttt	gctgcttaga	aatttcctct	540
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<210> 92

<211> 639

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (62)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (126)

<223> n equals a,t,g, or c

<400> 92

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gcagantcag	aatggggcctc	agcatcaggc	tcccaatcct	ggcttctaac	tgctgcgctc	180
tgcccttcyc	tcwccccacc	tccccactcc	agtgcctttg	gtcatgccac	tgcagctttc	240
aggccaatac	tggattagcc	tcttagtggt	cttgtccctg	cagccatttc	cccaggcagc	300
aattccatgt	gccctcactg	atgtagggtg	ctcttggtgc	atttgtcaca	tcctattgaa	360
ttgtttatgc	atcttggtca	cactcacagc	accctccctc	tcacacgtcc	tcctataaaa	420
aatgtccctc	agtgtctgct	atgagccagg	tgcagactta	agtgacagg	ctgctacggg	480
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<210> 93

<211> 858

<212> DNA

<213> Homo sapiens

<400> 93

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taagcccaga	atctcccctt	ccctgaagg	aggccagcac	cccaggagg	cagcaggtgt	180
gctgtgagg	ttggagtagt	gtgagaggtc	aggggtacact	agaatggcca	tggacaccat	240
gtgggggtgc	tctgggctgg	gccacagaac	agtgtccttc	ctgctgctcc	tcccctgcag	300
cttccccga	ccttggtggt	tatttggttt	gataccaatc	agcagaccct	gcaaggtgga	360

ggctcccagg	cctctcagtc	ccaccactct	catgtgccag	tcacccttac	tgtaactgcc	420
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gcagggccta	gggaatggat	gctgctgatt	ggctagggat	gcaatcatag	gggtgtagaa	660
aaggtccttg	tgcactgagt	ccacttttgg	gtgagagcta	ccaaggagct	gctggtctgc	720
tggtcccggg	agagccatct	ggtgtcagga	atgcaaaagt	gtggccaggc	acagtggccc	780
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tcgagggggg	gcccggta					858

<210> 94
 <211> 526
 <212> DNA
 <213> Homo sapiens

<400> 94						
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gttgtaaaac	tggaaaaaaa	ttttagaaga	catcttgtcc	agcatctgtg	tttatgtcta	240
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gtagcargc	ttggtctgg	gacctttcta	ctgaaccaca	gtgccgctgg	gggaagtcct	360
cagcacagat	ggctgctgct	atagctgggg	tatgggcagt	attagtagtt	aaccagtcaa	420
cccaagttcc	catagtctag	gttctgcttc	agctggagg	tagggaaaaa	cacaagaaaa	480
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<210> 95
 <211> 426
 <212> DNA
 <213> Homo sapiens

<400> 95						
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gaatgtcccc	agagacaaaa	gggaaaggta	gaccccttcc	cttaaagatg	aaagccatcg	180
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cttgcaagt	ctccgcgtcg	acctggcacc	tgggtgaarg	cttgctcttg	ctggtgcccc	360
tagccccag	tgtatggtct	tgamctcccc	agccatatgg	araccacact	caggagggcc	420
cctcga						426

<210> 96
 <211> 844
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (416)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (471)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (490)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (732)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (835)
 <223> n equals a,t,g, or c

<400> 96
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 tcagtgaagc atttggggst gctagctctg cctatgggtg aggtcagcta tctcacgcca 720
 tctacttcca cntgcccccc catgccaggc tcacctgag ctgagatgcc tgagcaggtg 780
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 tttt 844

<210> 97
 <211> 1985
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (332)
 <223> n equals a,t,g, or c

<400> 97
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 ctcttacctg gggcggtcca tgaagggtgca gtatgaggaa gtcgctgaga aagatgatct 180
 aatgggtgtg gaagatacag caaagaaagg attctyctca aagccatcgc tccgcagcag 240
 gaacaccatt ttcaccctag gaaccgcggc ctctgtcatc tccccactg aacttgaggc 300
 ccccatcctg gtgcctcaca cagcgcagcg gnagagcaga ggtatccatt tgaggccctc 360
 ttccgcagcc agcactacgs cctcctagac aattcctgcc gcgaatacct tttcatctgt 420
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gatctcagca	atttgaacac	taacctctcc	cctcctggct	caagaattac	tccgaagtca	1920
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<210> 98

<211> 1416

<212> DNA

<213> Homo sapiens

<400> 98

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gaagaatgat	ttgaatccta	tgtttctgga	tcaagtagct	aaatttatta	ttgataacac	180
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tcggtatgtt	ccgggctctt	cgggatcttc	taacacacta	cccacagcag	atcctttttac	300
agggtgctgg	cgttatgtac	caggttctgc	aagtatggga	actaccatgg	ccggagttag	360
tccattttaca	gggaatagtg	cctaccgatc	agctgcatct	aaaacaatga	atattttattt	420
ccctaaaaaa	gaggctgtca	catttgacca	agcaaaccct	acacaaatat	taggtaaact	480
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tgattcaaat	gctgtacaat	tagccaagtc	tttaggtgtt	gatttctcaa	taaaaaagta	1140
ttcctcagta	tcagaaccag	ctaaagtaag	tgaatgtgtg	agatttatcc	taaatttgct	1200
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gacatgactg	ataacagata	attaaaaaaa	gagaatacgg	tggattaagt	aaaattttac	1320
atcttgtaaa	gtggtgggga	ggggaaacag	aaataaaatt	tttgactgc	tgaaaaaaa	1380
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<210> 99

<211> 1760

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (255)

<223> n equals a,t,g, or c

<400> 99

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ctgtctcaaa	aaaataaaat	aaaataaaat	aaaaacaaag	aaaaaaaaat	aaaatcttta	180
ggcattccca	gacacaaaga	tctcagagac	agacaacaga	gagcytccgt	gttcatctgc	240
ccgaggctgt	ttgtncacag	ttcccttaaa	agatgcctgg	aaatgctccc	aacaacaagg	300
gactcaagta	tggggctgag	tttgttaaaa	aagcagctaa	atgtgtttag	gaaacacacg	360
aagtgaacc	agacagtgat	ggcccatgta	caagacttgt	gcttgaagct	ttgggtgtgcc	420
tccatggcca	atttttcagg	caccaaacc	cattcctgat	taattattgt	taaaaaagca	480
gctaaatgtg	tttaggaaac	acacgaagtg	aaaccagaca	gtgatggccc	atgtacaaga	540
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ctgattaatt	attgatatac	aatgcaaacc	aaactatgaa	aacacagact	ttttttcaga	660
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tattatttcg	gaggagaaga	accaccataa	agtatgagct	atccactggt	cctttttatg	960
tcatgtatgg	taatcagctc	atctccta	gcaggctcac	aaacttccac	gggtgagatgt	1020
ctaagtgact	tagtgacctt	cacactcatt	aaaggcagcc	ctgtccatca	aactccatac	1080
ctagaaagtt	caataaaactg	tattacattt	taataaatat	ktctgtgtac	tttttgtttt	1140
ttgcttttaa	gtcagctta	aattttgtca	aggaaacat	ttcacaagac	agtatgtcac	1200
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atataaatat	atattatatt	tacatttcct	tcttagcttt	caatttaggt	gagtgtattt	1320
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raacctgctt	gtttactcca	ttaacctgtt	taattaagat	ctgcttttaa	atgcctgatg	1680
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<210> 100

<211> 599

<212> DNA

<213> Homo sapiens

<400> 100

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aggtcgttgg	agggtggcagc	gagacatgca	cccggcccgg	aagctcctca	gcctcctctt	120

cctcatcctg	atgggcactg	aactcactca	agactccgct	gcccccgact	ccctgctgag	180
aagttcaaag	ggcagcacga	gggggtcttt	ggctgctatt	gtcatctgga	gggggaagag	240
tgagagccgg	atagccaaga	ccccaggcat	tttcagaggt	ggcgggacct	tagtcctacc	300
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tccagaaaca	ggcgggtggg	attgtgccgc	tgagacctgg	aagggcagcc	agcgtgccgg	420
ccagctgtgt	gcattgctgg	cttaatatgc	agggcttggg	gggctgtggc	cacatgcccg	480
gcaggaggtg	agtgaggagc	cctgtggcgt	gctgggtgtg	ggatcgtggg	catttcaaac	540
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<210> 101

<211> 784

<212> DNA

<213> Homo sapiens

<400> 101

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cttcttcctg	tcattgatcc	agactaatac	tctgggggtca	gcctcatttc	ttctctttct	180
cactttgcac	atccacttgt	caccaaatack	rgttcattct	gcacctaag	taagtccttt	240
gattcctcca	gttgttcatt	agtaatgtct	caartgtaat	tttttctagt	agttttcagc	300
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gatcawattt	tatttaaaaa	tactttacaw	akgtttatkg	ccaaatatta	graaatacag	420
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gatttttaatt	tttaaaaaatg	tatatttttt	cctgtgtaga	gtagtaacac	ccttgaaaac	540
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gatattttac	aatttcattt	atcaccacct	ttctctagcc	tttaccgctc	tcttcaatat	660
twacatatgc	agaagtttct	cctaacaaac	acctgcctct	gcctcagttc	tgctaccacc	720
ctgttgcttt	ctttcccttc	acaatcaaat	ttaagagtgt	caaaaaaaaa	aaaaaaaaaac	780
tcga						784

<210> 102

<211> 404

<212> DNA

<213> Homo sapiens

<400> 102

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ggctatgaaa	agaacttgaa	attgtcggaa	tatgtgtctc	cttcatgtca	tattcaatag	180
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ctttcaattt	ttaattttta	aagttttttt	ggtattaaaa	aatctattca	caagccaaaa	360
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<210> 103

<211> 760

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (438)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (741)

<223> n equals a,t,g, or c

<400> 103

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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa			760

<210> 104

<211> 1351

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (544)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (774)

<223> n equals a,t,g, or c

<400> 104

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ttaatcataat	acttgtcttt	tgtaaaatagc	agctttttgtg	tcattctccc	cactttatta	1260
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taaaacttat aatgcatgta aaaaaaaaaa a

1351

<210> 105

<211> 2066

<212> DNA

<213> Homo sapiens

<400> 105

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cacctctgaa	gttttgcagc	gcccagaaag	gagggcagga	aggaggaggt	gtgtgagagg	180
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ggattctgct	cgtgttccaa	atcatcgcct	ttctgggtggg	aggcttgatt	gctccagggc	360
ccacaacggc	agtgtcctac	atgtcgggtga	aatgtgtgga	tgcccgttaag	aacctacaca	420
agacaaaatg	gttcgtgcct	tggggaccca	atcattgtga	caagatccga	gacattgaag	480
aggcaattcc	aagggaatt	gaagccaatg	acatcgtgtt	ttctgttcac	attcccctcc	540
cccacatgga	gatgagtcct	tggttccaat	tcatgctgtt	tatcctgcag	ctggacattg	600
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<210> 106

<211> 1705

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (724)

<223> n equals a,t,g, or c

<400> 106

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<210> 107

<211> 1167

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (6)

<223> n equals a,t,g, or c

<400> 107

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<210> 108

<211> 1907

<212> DNA

<213> Homo sapiens

<400> 108

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<210> 109

<211> 611

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (19)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (21)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (47)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (607)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (610)

<223> n equals a,t,g, or c

<400> 109

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<210> 110

<211> 2632

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2620)

<223> n equals a,t,g, or c

<400> 110

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<210> 111

<211> 2249

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1579)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2226)

<223> n equals a,t,g, or c

<400> 111

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 <223> n equals a,t,g, or c

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 <223> n equals a,t,g, or c

<220>
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 <222> (640)
 <223> n equals a,t,g, or c

<400> 112

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<211> 1043

<212> DNA

<213> Homo sapiens

<400> 113

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<210> 114

<211> 703

<212> DNA

<213> Homo sapiens

<400> 114

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<211> 3684

<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2297)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (3679)

<223> n equals a,t,g, or c

<400> 115

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<211> 1965

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (476)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1136)

<223> n equals a,t,g, or c

<400> 116

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<211> 503

<212> DNA

<213> Homo sapiens

<400> 117
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<210> 118
 <211> 1071
 <212> DNA
 <213> Homo sapiens

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 cccagctccc tttgacctct ggggcagggc agggggcagg gagagacaag gctgctgcta 780
 ttagagccca tcctggagcc ccacctctga accacctcct accagctgtc cctcaggctg 840
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 tgtgtgtgtg agagtgtgaa tgcacaggtg ggtatttaat ctgtattatt ccccgttctt 960
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 aaaaaaaaaa aaaaaaaraaa raaaaaaaaa aaaaaaaaaa aaaaaaaaag g 1071

<210> 119
 <211> 1101
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (147)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (376)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (395)
 <223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1101)

<223> n equals a,t,g, or c

<400> 119

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ccgggggctg	ggcctgtccc	acagggncgt	ggagctcgtg	gttctgagca	gccagctggg	180
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ggggcacagg	gccagtggg	ccggccacgc	tcgggcccctc	acctgtgaga	tggggtcgga	360
atttkacaca	gcctanggct	tggttcttgg	tkgtngameg	tggactyctk	agaacgggag	420
tgctggtcct	gaaaggcgtg	gttgagacc	agctgctttt	ctcgtgttt	ttctcttagg	480
agattaaaca	aaaacagaaa	gcacaagacg	aactcagtag	cagaccccag	actctcccct	540
tgccagacgt	ggttccagac	ggggagacgc	acctcgtcca	gaacgggatt	cagctgtctca	600
acgggcatgc	gccggggggc	gtcccaaacc	tcgcagggtc	ccagcaggcc	aaccggcacc	660
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gccacggggc	gctggggctg	gtgtgggtgg	gccttgtgtg	ctggatttgt	agcttatctt	1020
ccgtgttgtc	tttggacctg	ttttagtaaa	cccgtttttc	attttaaaaa	aaaaaaaaaa	1080
aaactttggg	ggggggcccc	n				1101

<210> 120

<211> 282

<212> DNA

<213> Homo sapiens

<400> 120

agcttctctg	tccagtcttg	aactctgggs	tctcttgga	ctttcctcac	ccctctcagc	60
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accttatctt	tgcaatatgt	tcgggcccac	cttccactcc	ttggttcttg	ttcctccttg	180
gcctaacttg	tcccttctcc	acttcacatc	cccggtgga	cagcattcct	ccttcctccc	240
aacctccctc	cgtctcaraa	aaaaaaaaaa	aaaaaaaaaa	tt		282

<210> 121

<211> 2635

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2605)

<223> n equals a,t,g, or c

<400> 121

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agagagagct	gtccctgaga	ccccggagag	aagcagctgc	cgaagctgc	agcctttccg	120
cactctgaga	ccatgatctt	cctcctgcc	ggggagagcc	acccacaggc	catgtccagc	180
cccacttccc	tcagcccca	gggyttcctt	ctggcccctc	tgaggattcc	ctagggctgc	240
cccgcagagg	ggyttcccca	agctctgttt	tgaagcctgc	aatgtggaaa	agtgagaagt	300
cagagggaac	aggacagggtg	cagccgggct	ctgaggccac	acctcacacc	tcgtgttcc	360
ccaacatccc	ctgagcagtg	tgagctcatc	tcaccagatg	agaagaggcc	ctgtgcattt	420

yttttgtttg	tttgttctg	ttttccccc	cccatccagt	tctcctcagc	aaagcaaatt	480
ccttaacacc	tttggaggag	aatttcttac	ccagacttgg	ggctgtgatg	cccttcagtg	540
cgtggtgagt	gcagcgtgtg	tgcgtgtgcc	tggtgtgtgaa	cctggggggcc	atcctgggtg	600
cctgggagcg	tgaggagagg	ccccctgtgt	gctgggtgag	tggtgggtgt	gggggtcaatg	660
cagtggaggct	ctctgggtga	ggctcccaac	ctggcagtc	ccagcctccc	agcatctgtg	720
agcgtctgtt	ggactttaca	gaagagcctc	atccygtctg	cccctcactc	tgccctggaa	780
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tcagagagg	tccaagggtg	atggagaagg	aagcatggcc	tgggagcttg	gaaggargg	1860
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acatgcataa	aggaatcaa	atgttatttt	taagaaaatg	gaaaaataaa	actttataaa	2580
caccaaaaaa	aaaaaaaaaa	accnnggggg	ggggccggta	accatttctg	cctaa	2635

<210> 122

<211> 994

<212> DNA

<213> Homo sapiens

<400> 122

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aagcacagga	gtaggggaga	tatacagcgg	tcaggataag	ggggaaagg	cggtggttg	120
scaagaggtg	aaacaagatg	tgagagacaa	ggggtaggga	agaaatggg	cagcggttag	180
gttcagagtg	gcatagaccg	tggcggacgg	gcaatgcgag	gggcacagaa	aggaactgag	240
gggtgggcta	ttttaargga	gatggtcctt	cagccctctt	yttttctgcg	tagttctcct	300
cctccaggcc	gcgcgcggat	atgtcgtccg	gaaaccagcc	cagtctaggc	tggatgatga	360
cccacctcct	tctacgctgc	tcaaagacta	ccagaatgtc	cctggaattg	agaaggttga	420
tgatgtcgtg	aaaagactct	tgtctttgga	aatggccaac	aagaaggaga	tgctaaaaat	480
caagcaagaa	cagtttatga	agaagattgt	tgcaaaccac	gaggacacca	gatccctgga	540
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tcgaaaggac	aaagcccaca	aacgctatct	gctaattgagc	attgaccaga	ggaaaaagat	660
gctcaaaaac	ctccgtaaca	ccaactatga	tgtcttttag	aagatatgct	gggggctggg	720
aattgagtac	accttcccc	ctctgtatta	ccgaagagcc	caccgcccga	tcgtgaccac	780

gaaggctctg	tgcattcggg	ttttccagga	gactcaaaag	ctgaagaagc	gaagaagagc	840
cttaaaggct	gcagcagcag	cccaaaaaca	agcaaagcgg	aggaacccag	acagccctgc	900
caaagccata	ccaaagacac	tcaaagacag	ccaataaatt	ctgttcaatc	atttaaaaaa	960
aaaaaaaaaa	aaaaaaaaaa	aaaaagggga	gggg			994

<210> 123

<211> 2537

<212> DNA

<213> Homo sapiens

<400> 123

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tcgtagtcca	ccccctcccc	atccccagcc	cccggggatt	caggctcgcc	agcgcccagc	120
cagggagccg	gcccgggaagc	gcgatggggg	ccccagccgc	ctcgctcctg	ctcctgctcc	180
tgctgttcgc	ctgctgctgg	gcgccggcg	gggccaacct	ctcccaggac	ggctactggc	240
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tctggagcag	ccctgacatg	ctggccagtc	aagacagcca	gccctggaca	tctgatgaaa	360
cagtggtagc	tggtggcacc	gtggtgctca	agtgcgaagt	gaaagatcac	gaggactcat	420
ccctgcaatg	gtctaaccct	gtcagcaga	ctctctactt	tggggagaag	agagcccttc	480
gagataatcg	aattcagctg	gttacctcta	cgccccacga	gtcagcatc	agcatcagca	540
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aatcttcatt	acgggaaaaa	gacacagcca	ccctaaactg	tcagtcttct	gggagcaagc	720
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cccgggagga	tgatggggcg	agcatcggtg	gctctgtgaa	ccatgaatct	ctaaagggag	900
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cagaccctcc	ccatcctcgt	gagggccaga	agctggtgct	acactgtgag	ggtcgcggca	1020
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cccaggagag	tgccctgata	ttccctttcc	tcaacaagag	tgacagtggc	acctacggct	1140
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ccagtccggg	gccctcctcc	tccagcacct	accacgccat	catcggtggg	atcgtggcct	1260
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<210> 124
 <211> 1390
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (498)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (499)
 <223> n equals a,t,g, or c

<400> 124
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 ttcccgggtc gacccacgcg tccgggcctc aggggtggacg catggttctg cactgaggcc 120
 ctcgctcatgg tggcgccctgt gtgggtacttg gtacgggcgg ctctgctagt cggctttatc 180
 ctcttcctga ctcgacagccg gggccgggcg gcatcagccg gccaaagagcc actgcacaat 240
 gaggagctgg caggagcagg ccgggtggcc cagcctgggc ccctggagcc tgaggagccg 300
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 gctaagaaac tgccggaannt ggaggagaaa caagcgcgaa aggccagck tgaggcagag 540
 gaggctgaac gtgargwgcg gaaacgactc gagtcccagc gcgaatgagt ggaagaagga 600
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 aggtgtgatt gacgaccggg gcaagttcat ctacataacc ccagaggaac tggccgccgt 960
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 ctccctcatc gcctggggcc gggagtcccc tgcccaagcc ccagcctgac cccagtcctt 1080
 ccctcttgga ctcagagttg gtgtggccta cctggctata catcttcate cctccccacc 1140
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 gagcttggtg tggcttggtg tggcagaagg cctggcctag gatcctagat aagcaggtga 1260
 aatttaggct tcagaatata tccgagaggt ggggaggggt ccttggaagc tgggtgaagtc 1320
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 aaaaactcga 1390

<210> 125
 <211> 1288
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1286)
 <223> n equals a,t,g, or c

<400> 125
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 gacgctgacc acgttcctct cctcggctct ctccgcctcc agctccgcgc tgcccggcag 120
 ccgggagcca tgcgacccca gggcccccgc gcctccccgc agcgggctcc cggcctcctg 180
 ctgctcctgc tgctgcagct gccgcgcgcg tcgagcgctt ctgagatccc caaggggaag 240

caaaaggcgc	atccggcaga	gggaggtggt	ggacctgtat	aatggaatgt	gcttacaagg	300
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caaagctaaa	tatgtttaca	gaccaaagt	tgatttcaca	tgtttttaaa	tctagcatta	1020
ttcattttgc	ttcaatcaaa	agtggtttca	atatttttt	tagttggtta	gaatactttc	1080
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ctcttagtat	agcattttta	aaaaaatata	aaagctacca	atctttgtac	aatttgtaaa	1200
tgtaagaat	tttttttata	tctgttaaat	aaaaattatt	tccmacaacc	ttaaaaaaaa	1260
aaaaaaaaaa	aaaaaaaaaa	aaaaanaa				1288

<210> 126

<211> 1517

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (159)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1123)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1510)

<223> n equals a,t,g, or c

<400> 126

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aaacattcct	tcctaaatcc	tttattatat	tgaatatcgt	attaattggt	tttcagaggt	120
taaattaacc	atgtattcct	gcaataaatg	tcacttgtnt	cttgtatata	atctttttta	180
tatattaccg	gattgattca	ttagtatttt	gttgaggatt	tttgtgtcta	tattcataag	240
agatgctggg	ctgcagtttt	ctttttttgt	gataatctgg	tttttgtatc	agtaatacag	300
gccccatgaa	acgagttggg	aagtgttcac	ctctcttgta	ttttttcaag	agtttgtgaa	360
gaattgctat	taattcttta	aatgtttggt	agaatctacc	attgaaatca	tgtgtcctgg	420
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tctgtcaatt	gcaggctgct	aactaagcag	cccaggtcca	aatgaggcaa	aaacctttgc	780
ttttaacaca	tagtatagct	ttgtaatcct	tttcttgca	actcgggtaa	tttcttctct	840
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gctaattggt	tgtcaatttt	gttgatcttt	tgaaraacia	acctttggtt	ccactttctt	960
gttgcatatg	ctgartattc	tcataattgg	agtggaaagc	tgatctttga	ttacttattt	1020

tacttagggc	tgaggagttc	atggacttcg	caaaacctcc	ttgaatctaa	attgcatctt	1080
ctttcctggg	ttctgggctg	aaacatgttt	tttcccatct	wanawaccct	tggtcttttc	1140
atkggcgatt	aagactagag	aaagttctag	atmccttgtc	cttttatgct	gtcattttgt	1200
ttaaaggctt	tctatgtagt	aaaactatct	atatagacaa	aatagagcct	tgagttgtgg	1260
tcttgaattt	gatcaacatg	atttaccaca	ttctgtactg	gatatttctt	cacctgctgc	1320
tactgtaaac	cattttattc	ttggatcttc	tgtagagtat	attatcacag	gtacttttta	1380
caggggtgtc	taatcttttg	gcttccttgg	gcacattgaa	agaagaagaa	ttgtcttggg	1440
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<210> 127

<211> 1073

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (495)

<223> n equals a,t,g, or c

<400> 127

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cacaggcctt	tttgcaaatg	tgtaacctgc	ctatcaaagt	agtttgtagg	gcaaatgcag	180
aatatatgtc	tccatctggg	aaagtacctt	wtaytcatgt	gggaaatcaa	gtagtatcag	240
aacttgggtcc	aatagtccaa	tttgttaaag	ccaagggcca	ttctcttagt	gatgggctgg	300
aggaagtcca	aaaagcagaa	atgaaagctt	acatggaatt	agtcaacaat	atgctgttga	360
ctgcagagct	gtatcttcag	tggtgtgatg	aagctacagt	agggrmgatc	actcatgmta	420
ggtatggwtc	tccttaccct	tggcctctgw	wtcataatctt	ggcctatcaa	aaacagtggg	480
aagtcaaacg	taagntgaaa	gctattggat	ggggaaagaa	gactctggac	caggtcttag	540
aggatgtaga	ccagtgtctg	caagctctct	ctcaaagact	gggaacacaa	ccgtatttct	600
tcaataagca	gcctactgaa	cttgacgcac	tggtattttg	ccatctatac	accattctta	660
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attagatatt	ggtgtcagaa	ttttaaaacc	aaattactgc	tttttgaaac	ctcaaattat	900
ataatgtatc	ttatgtatgt	gctttatatt	gttattttgt	tatacattaa	aataattctg	960
aattatttaa	tctgatatgt	tgtattctgt	atcttgaaat	ttttgtttcc	ttgaaacatg	1020
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<210> 128

<211> 300

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (273)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (294)

<223> n equals a,t,g, or c

<400> 128

80

caacccctgc	cttttttttg	ttttccattt	gcttggtaga	tcttcctcca	tccctttatt	60
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tcttgactct	gtatccaatt	tgccagctcg	tgtctttcat	ttggagcatt	tagcccattt	180
acattttaagg	tkaatattgt	tatgtgtgaa	tttratcytr	tcattatgwt	gttagctggg	240
tattttgctt	gtaggtgat	gcagtttctt	ccnggcacat	atggtcttta	caanttggca	300

<210> 129

<211> 1275

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1152)

<223> n equals a,t,g, or c

<400> 129

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ctcttttgc	tttccctttc	ttcctggtag	cccctgcccc	ttcctgtatt	ttctcccatc	180
gccatttctc	cctctcccac	tgtccctaac	cggttcaaac	tctttcctct	taaatgggtg	240
agattttctc	tcaccaagca	caccccagta	ttaattaaac	tagctgcaaa	caggcagcaa	300
gtgggtctacc	atgacagatg	ggttttgtgt	gtgtgtgtgt	gtgtgtaatt	gtaataaaac	360
atattgartc	actcaataaa	cacagagtgt	ctactacatg	tatcargcac	tatcatagat	420
gctaattaac	gaaactgaaa	tggccaggcc	ctcacagtgg	ctcatgccta	taatcccagc	480
actttgggag	gatgaggcag	gaggatcact	tgaggccggg	agttcaagac	cagcctgggc	540
aacatagtaa	gactccatct	ctacaaaaaa	aaaatttttt	ttattatact	ttaagttttg	600
ggttacatgt	gcagaacgtg	tagttttggt	acataggtat	atacgtgccc	tggtagtttg	660
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catccctttt	tatgggtgca	tagtgttcca	tgggtgtatac	gtgccacatt	ttcttaatct	960
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tttgaactaa	tntacactcc	caccaacagt	gtaaaagtgt	ttctattttt	ccacaacctc	1200
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<210> 130

<211> 472

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (471)

<223> n equals a,t,g, or c

<220>

<221> SITE
 <222> (472)
 <223> n equals a,t,g, or c

<400> 130
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 gctagcagtt agtgttgtag agaagacaga tatttggtgca tttgtgcatt ttctaagttt 180
 gctgcaatga gcatgtatta ctttcatagt tataaaacac atgcaaaatg ccctttttaa 240
 atgaaaaaaaa atccatgagt gtaagtata tataatgttt ggaaagcctg ggacgggtcat 300
 tgtttactct caatagtatg tgtttgcctt tgtctttttg agacattttg ttttaactcg 360
 ttgatgacaa taacctgttg ataataaac ttgataacaa ataaatgac ttatgattga 420
 awmaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nn 472

<210> 131
 <211> 1950
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (132)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (225)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (249)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (577)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1933)
 <223> n equals a,t,g, or c

<400> 131
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 cttctggaac cttttgtggt atttccaacg gctacgntcg ccagttatgc taccaggcct 600
 ggtgctggcc tcctgtgatg ggccctcgma ctcccaggcc ccatctcctt ggctaaccct 660
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cactggcctg	cacctgcaga	ggggaatcta	ccgtgagata	ttattcctga	caatggctgc	960
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taatttttct	tgctgcccc	gccttgggga	atgcctcacc	cacccaggctc	ctgacctgtg	1860
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<210> 132
 <211> 990
 <212> DNA
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (657)
 <223> n equals a,t,g, or c

 <220>
 <221> SITE
 <222> (852)
 <223> n equals a,t,g, or c

 <220>
 <221> SITE
 <222> (859)
 <223> n equals a,t,g, or c

 <220>
 <221> SITE
 <222> (962)
 <223> n equals a,t,g, or c

<400> 132						
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agcctgatct	ttttcatatt	agtatatgta	cattagctgc	ctgtggatta	acattttccat	180
gaaatgtatt	tttgcatgtg	ttgatcttaa	actttttgtg	tctttatata	aggtagcty	240
cttttaagca	tgatattttt	aaccacaata	gttgaaagac	aatctycacc	ttttacttgt	300
atattttacat	gtaatgtaat	ttttgatgca	tattacgtct	tattatttaa	ccaacctatt	360
ttattttatc	tagggcattt	ttcagaaagc	cttattttct	tgtattaatc	aaatattttt	420
aycattgtat	tttccyctat	tagttagkaa	tacgktacyc	yaaatatata	ttgtggstat	480
tttcagaatt	gcaatatgcc	tccttaattt	attagaggct	aacctaaatt	attactttta	540

ccacttactt	gaaaattctg	gaactttaga	acattttattg	ttttatgcat	tttaattcta	600
cttgatattt	tactactcct	aaacattatt	attgttttag	acaagccaaa	atataatntg	660
ttattatctt	atctccatt	tctttctgta	tttttatgcc	actatgtatg	ctcaatttcc	720
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gcatatagaa	tnctaggtn	acatattttt	agtattttata	aatgtaaagt	cattwattkg	900
gcttctatca	tttckgtkga	gaaatcaatt	gtcagcccaa	tagtttttca	ttttaaatta	960
cngaattttt	tcattgtctct	ggttttagga				990

<210> 133

<211> 1720

<212> DNA

<213> Homo sapiens

<400> 133

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ggatatagag	actcaacagt	gacatttatt	gtacaacatc	aaggggaata	ggatactcat	180
caaaactggga	ttattcttat	caaaacatgg	tcttctttga	ataagaaaaa	tacatagtgtg	240
gttattatgg	acttaaaact	gtgttaaatg	gatattctga	taaaatattt	gctgctctgt	300
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gtacgccgat	ggtttcatat	taactaaaaa	agctgggtat	tgtaaaatct	catttataaa	420
aactcagatg	agaagaaaat	tttctttgat	ggtgagactg	ttgtcttagt	tcaggaaatt	480
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aaaatatgta	atattttata	tgttatacca	tgatcatatat	acttgcaata	tcagaccttg	1620
cattcaatat	acaatgcaat	tgactctttg	cagacctgca	tttttcagtg	aacaataaaa	1680
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<210> 134

<211> 705

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (349)

<223> n equals a,t,g, or c

<220>

<221> SITE
 <222> (409)
 <223> n equals a,t,g, or c

<400> 134

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gtggaatcac	agacactcct	agaggagaat	gctgttcaag	gaacagaacg	tactcttgga	180
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tcctcattgc	cctgtatacc	tttaagcaag	ccagtggaa	tcttaagact	agatttaattg	300
actccgtatt	tgaacacctc	taacagagaa	gtaaaaggtat	acgtttgttna	aatctgggaa	360
gacttgactg	ctattccatt	ttgggtatca	tatgtacctt	gatgaagang	attaggttgg	420
gatacttcaa	gtgaagcctc	ccactggaaa	caagctgcag	ttgtttttaga	taatcccatc	480
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atcacagtaa	agcaatgaag	agcagttttc	caatgaaaac	tgtgtaaata	gagcatcaac	600
aagtacaaaa	ttcttgtctt	aattagtggg	ggtatataaa	aattccttgt	aatgggtcaaa	660
tatttttttaa	aattgacatt	aataaagcat	attttaaaag	tttct		705

<210> 135
 <211> 323
 <212> DNA
 <213> Homo sapiens

<400> 135

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gtatttctgt	tcctcagttt	tgccctgggga	aatggaggst	cagtgacgtt	cagtgacgtg	180
cccagagtca	tgccattggc	gggtggccca	gkgmtccagg	tctccagcac	ccctcggcc	240
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aggaaaaaaa	aaaaaaaaaa	aac				323

<210> 136
 <211> 582
 <212> DNA
 <213> Homo sapiens

<400> 136

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gaatctkgac	cctttacca	ctaattttga	aggaaagatac	cttggaata	tttggcattc	180
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aaaaccagat	taaggtttga	ctgggtttcat	ttgattttta	ag		582

<210> 137
 <211> 1021
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE

<222> (248)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1004)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1014)
 <223> n equals a,t,g, or c

<400> 137
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 gactctctcc tggagtccag agcaccttgg aaccaagtac agcgaagccc actgagttca 600
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 aacccgacag actcagggtc crgcagcttc cctggagcag tcctctccat ccytgggaca 720
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 agccttagat agcagcagaa ggcttttttg attctcctcc ttgaaaagat tctcagttac 960
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 a 1021

<210> 138
 <211> 1777
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (58)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (118)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (237)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (661)
 <223> n equals a,t,g, or c

<400> 138

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tagctcactg	cagccttgaa	ctcctgggct	caggcaatcc	tcctacctta	gcctcctgag	180
tagctaggac	tacaggaatg	tgccatcatg	cctgggtaat	ttttaagttt	tttgtanaga	240
tgggatctca	ctatgttgcc	caagctgggt	tcagattcct	gtgctcaagg	gattctgcta	300
acttggctcc	ccaaagtgtc	gggattacaa	atgtgagcca	ctgtatctgg	cccatattct	360
tttttaagaa	aaagatgcag	aggtgttaaa	tattaatatc	aaattgtcca	ggcatgggtg	420
ttatgaaatt	gtgtgccctc	tgacaggcaa	ccaaacacac	acgacttcat	ttctttatta	480
attcctgcct	catcatcttt	tctcattgat	gctccttaat	gtcaaaaggaa	tctctctctc	540
tcacacacac	ataagaccaa	aacaaatatc	ttgaacatgc	aaaaaaatag	tctacgcttt	600
tgaatagtgt	gcactgttga	atagtgtgca	ctgttgata	gtgtgactg	ttgaagtgtg	660
natgtgccta	aggcaacagg	atcttgggaa	agctctagat	ttttggcytc	gaaataaaac	720
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aatactatct	acgctgagtt	atctattgcc	aactagcacc	aattctccaa	atcaaagtgt	840
gtgaggaaaa	cacactcgtg	caatcctctt	taacagaaga	tacaccaagt	aacctgtctg	900
tctacttctg	ttaccagaa	ataaaagaac	ttgaagggtc	gcttggctgg	aggggtccgg	960
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cctcgggctg	ctcctcttcc	acataattga	atttcaattc	tggaaatttc	ttcagtctgt	1140
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ttgtctcgtg	tcctagtcac	gttgtattga	atggttctta	ttaccaccag	gatcaggaga	1680
ctcccccaagg	agatttccagt	taaaactcgt	tctgaatacc	aagtaatatt	ttttagtagc	1740
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<210> 139

<211> 643

<212> DNA

<213> Homo sapiens

<400> 139

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ttcattgtgg	ggagcggggc	gatgtccagc	ctcagaactt	ctggaactgc	ttcttgggtc	120
cggcagcctt	ggtgaccttg	agcacgttga	agcgactgt	cttgctcaga	ggccggcact	180
cgccactgt	gacgatgtca	ccgatctgga	cgtccctgaa	gcagggggac	aggtgtacag	240
acatgtttct	gtggcgcttc	tcgaagcggg	tgtacttgcg	gatgtagtgc	agatagtctc	300
ggcggatgac	aatgggtectc	tgcatcttca	tcttgggtca	ccacgccaga	gaggatccgc	360
cctcgaatgg	acacattacc	agtgaagggg	catttcttgt	caatgtaggt	gcccctcaat	420
agcctccttg	gggtgtcttt	gaagcccaga	ccgatgttct	tgtagtaac	ccgcgggagc	480
ttctccttgc	cagtttcttc	cagcaggacc	ctcttcttgt	tttgaaagat	ggtcggctgc	540
ttttggtagg	cacgctcagt	ctgaatgtcc	gccatcttct	cgtgccgmay	tcctgcagcc	600
cgggggatcc	actagttcta	gagcggccgc	accgcggtgg	agc		643

<210> 140

<211> 1220

<212> DNA

<213> Homo sapiens

<220>
 <221> SITE
 <222> (404)
 <223> n equals a,t,g, or c

<400> 140
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 tcctggctca ctgcaacctc tgccctcctag cttcaagggg ttctcctgcc tcagcctccc 120
 gagtagctgg gattacacgt gcccaccacc acgcccagact aatattkgta ttttttagtag 180
 agacggggct tcaccagggt ggccaggcta gtcttggaac tcctgacytc gtgatccacc 240
 tgcytcggcy tcccaaagtg ctgggattac aggtgtgagc cgtcttggtg tttttgtttt 300
 tgtttgtttt taaaagatgg artttcactc ttattgcccc ggctggaktg caatggcacr 360
 atctcggtc accgcaatct ccacctcctg ggctcaagca attnttctgc ccagcctcc 420
 caaagtgtg gaattacagg tgcccggcac catgcccac caattttcsg taytcytagt 480
 agaggtgggg tttcacaacg tkggccaggc tggtytcaaa ctcaaaytcc tgacytcagg 540
 tgatctgccc actttggcyt cccgaaatgc tgagactaga ggcgcgagcc accacgcctg 600
 gcctacaaac acattcttgt ttgggttttt atataaaaata tgagcacaaa aatactttcc 660
 ctaaatacag cctctggctt tgcctaacc ttggcacaca sccaagtacc tcttccattc 720
 tcagatagct gaggggagtg tatagagggt tagagtacat acgtttcttc tccaactctt 780
 cgctgtctag aagaagacta accacctctt tgggtttcaa ggtatctggt ttgaagttcc 840
 cacctgaaat caccatccgc tgaatctcac tcttctcctt ggctctttgc agaatgcgtt 900
 cttcaatggt gcctttacag atgagccggt acacagtaac ctgctttgtc tgccctaagc 960
 ggtgggacct gtccatggcc tgctggtcca cagtggggtt ccagtcgcta tcatagaaaa 1020
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 aacacaaaga tgtcattcct gttctgaaaa tcagcaacca tgtctgcct ctcgagatc 1140
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 aggtctatca tcctcgtgcc 1220

<210> 141
 <211> 721
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (623)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (626)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (638)
 <223> n equals a,t,g, or c

<400> 141
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 ggggtcctt atgcacagcg gggcgtctcc ttgtggccat agaaacggaa ctggctcttt 120
 tcaacagtgc tgcaagagga tggttattta acgctggccc ccaaggagga aaggcacaga 180
 cyttcctccc tcctggaaca tccaagggca ctggatcctc tgtgtccctc tgagatgggg 240
 tgccactcca gcaagagcac cacggtggca gctgagtcct agaagcttga agaagagyg 300
 gaggggaagag agccagggtc ggagaccggc acccaggcag cagactgcaa ggatgcccc 360
 ctgaaggatg gaacccctga gccaaagagc tgaaatgcct ctctccagag tcggaccctc 420
 acctcyttcc tggaaactgcc tttggcccca gaaccatgag acaatcccca ccctgagaag 480

ctccgatcac	tgggaggaga	gagaaagcct	ccagcttttg	gattcaggct	tcagaagttt	540
ttagcagcct	ttgctcattg	gagagggtgg	gaaaggataa	agttcttata	aggaaatccc	600
taatttcccc	cagctcctcc	ccnccngaag	aaggaacnaa	agaaaagttcc	ttccacacgt	660
tttggtggaa	acttttccct	tgccaacttt	ccttggtattg	ccagaacaaa	gccctccaga	720
a						721

<210> 142
 <211> 1468
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (901)
 <223> n equals a,t,g, or c

<400> 142						
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gttttattct	caaaatatag	agattctgtg	atttatttgc	cctgtttatg	gattaaaaag	180
aaaattctaa	tataaagcat	ttcaatagga	tgcataggtg	tattacgttt	tttaaatgct	240
ttagatctgt	gattcttgac	ttactattta	ttttatcccc	tttaagtcag	ggatgcttta	300
ttctatttta	aagcacttat	gagttacatg	ttgtaatcaa	gtttgcacaa	tatatatttc	360
tatatgagga	accataaat	gaatagctaa	tttttaaaat	gccattaaaa	tgcatgaaat	420
kcttattaaa	accttactat	actatttctt	caaggcaagt	aaattgacca	tgrgraaagr	480
acacagttat	taaacactgt	tgacaggaaa	attctccttg	ataacatagg	acaattaatg	540
gaaaaaaaaa	ttctcattat	ttgcaaagaa	tgaacaagtt	aatgaacaaa	caaactagat	600
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ttgagaaatc	agatagcaat	atagacattc	acagcagctc	tgtggatacc	atgtaattgt	720
caggtaattt	cagaatgttg	aaaattattc	agtgcagccc	tcatagtatc	atacttgaag	780
aaattgatta	cagttccact	aaattgttga	agataaatta	tttttaaaagg	ttatgaaaac	840
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agaataattg	ttaaaaatta	agcttttagg	tattagaagc	tgttataaaag	tataaaatta	1020
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gtacatatat	tactaagttg	cctctcccag	tttactttaa	aaatggcttt	aaggataaaag	1140
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aatttggaat	tgtgtctttt	atgttccatc	ctctgttggt	actagattta	gtttaaaaat	1380
tgtgtatgac	cattaatgta	tgtcataaac	atgtaaataa	aagatgttga	atcttgttga	1440
aaagcawraa	aaaaaaaaaa	aaactcga				1468

<210> 143
 <211> 300
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (268)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (284)

<223> n equals a,t,g, or c

<400> 143

tgaatttttt	gccaaactta	gtaactctgt	taaatatttg	gaggatttaa	agaacatccc	60
agtttgaatt	catttcaaac	tttttaaatt	tttttgact	atgtttggtt	ttattttcct	120
tctgttaatc	ttttgtattc	rcattatgctc	tcgtacattg	agtactttta	ttccaaaact	180
agtgggtttt	ctctactgga	aattttcaat	aaacctgtca	ttattgctta	ctttgattaa	240
aaaaaaaaaa	aaaaaaaaaa	aaaccccnag	ggggggggcg	ggtncccaat	cccccccaa	300

<210> 144

<211> 2243

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (929)

<223> n equals a,t,g, or c

<400> 144

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tcccccttct	agctccatgg	gactcgcccc	aagactgtgg	cttcaaggac	caccagcccc	120
ttactcttca	agccctgact	gtggagttgg	tagatgcctc	tgatcctcag	tattctctct	180
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cgtgttgcaa	tccctgctgc	cccttagcca	cccagggctc	tgtgtgggta	tgagtgtaga	300
ggatgggggt	atgccaggcc	tgggcccgtc	caggcaggcc	cgctggaccc	tgatgctact	360
cctatccact	gccatgtacg	gtgcccattg	cccattgctg	gcactgtgcc	atgtggacgg	420
ccgagtggcc	ttycggccct	cctcagccgt	gctgctgact	gagctgacca	agctactgtt	480
atgcgccttc	tcccttctgg	taggctggca	agcatggccc	caggggcccc	cacctggcg	540
ccaggctgct	cccttcgcac	tatcagccct	gctctatggc	gctaacaaca	acctggtgat	600
ctatcttcag	cgttacatgg	accccagcac	ctaccagggt	ctgagtaatc	tcaagattgg	660
aagcacagct	gtgctctact	gcctctgcct	ccggcacccg	ctctctgtgc	gtcagggggt	720
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cactccgcta	ggcctgctgc	tcctcattct	gtactgcctc	atctcaggct	tgtcgtcagt	900
gtacacagag	ctgctcatga	agcgacagng	gctgcccctg	gcacttcaga	acctcttctt	960
ctacactttt	ggtgtgcttc	tgaatctagg	tctgcatgct	ggcgccggct	ctggcccagg	1020
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gtctcctcca	gttccagcaa	tgccatagaga	catgctccct	gccctctcca	cagtgtctgt	1860
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gagtgaacctg	agaccaggta	caggaaacct	gtagctcaat	cagtgtctct	wtaactgcat	2160
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aaaaaaaaaa aaaaaaactc gag

2243

<210> 145

<211> 1082

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (265)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (354)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1064)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1081)

<223> n equals a,t,g, or c

<400> 145

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aaccatctcc	cacaattaat	tcttgactat	ataaatttat	ggtttgataa	tattatcaat	180
ttgtaatcaa	ttgagatttc	tttagtgctt	gcttttctgt	gactcaactg	cccagacacc	240
tcattgtact	tgaaaactgg	aacancctgg	gaatgccatg	gggtttgata	atctgccagg	300
gacatgaaga	ggctcagctt	cctgggacca	tgactttggc	tcagctgatc	ctgnacatgg	360
gagaacaacc	acatttttct	ttgtgtgtgc	ttctagcagc	tgttcgggag	gaccktgacc	420
caayagtgtt	cccatgctgt	ttcttgtgaa	atgctctcgg	ctatgtagca	gcttttgatt	480
ccctgcatac	cctaggctgc	tgcccctatc	ctgtcccttg	tttataacat	tgagaggttt	540
tctagggcac	atactgagtg	agagcagtg	tgagaagtcg	gggaaaatgg	tgactacttt	600
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tgctatthtt	gtgggttttg	ttctcccact	atggtaggac	ccctggccag	cattgtggct	960
tgtcatgtca	gccccattga	ctaccttctc	atgctctgag	gtactactgc	ctctgcagca	1020
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ng						1082

<210> 146

<211> 4313

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1126)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (4015)

<223> n equals a,t,g, or c

<400> 146

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cgcttcggg	ttaggccgtt	cctgcccgcc	ccctcctctc	ctcccttcgg	acccatagat	120
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<210> 147

<211> 1183

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1053)

<223> n equals a,t,g, or c

<400> 147

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<210> 148

<211> 734
 <212> DNA
 <213> Homo sapiens

<400> 148
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 <212> DNA
 <213> Homo sapiens

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 <223> n equals a,t,g, or c

<220>
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 <222> (842)
 <223> n equals a,t,g, or c

<220>
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 <222> (1079)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1334)
 <223> n equals a,t,g, or c

<400> 149
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<210> 150

<211> 2890

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (45)

<223> n equals a,t,g, or c

<400> 150

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<210> 151
 <211> 2399
 <212> DNA
 <213> Homo sapiens

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 <223> n equals a,t,g, or c

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<210> 152
 <211> 802
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (105)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (730)
 <223> n equals a,t,g, or c

<220>
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 <223> n equals a,t,g, or c

<220>
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 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (777)
 <223> n equals a,t,g, or c

<400> 152
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 tttttcctaa agaataacwt gaycctttgc caracggact acgaggaagg tttaatgaaa 180
 gaagggttatg caccctmgtt tgcgtgatct atcaacatca ccccatag aatacaaaagc 240
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 tatgtagtga aattgcccc agttcagagtt gaattgtttat tattaagaa aaaagtaatg 420
 tacatatggc tggatttttt tgcttgctat tgcgttttgt gtcacttggc atgagatgtt 480
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 tattgtgtta ccatttgtgt tccatttgct yctttgtatt gttgcattta gtacaatcag 600
 tgtttaaact tactgtatat ttatgctttc tgtatttacc agctatttta aatgagctgt 660
 aactttctag taaagaattg aaaagcaaat cctcactaaa ggatacacag gataggataa 720
 agccaagtcn catcaacatt aaaaaatact aaaaananaaa acacaaaaaa aaaaaanccc 780
 gggggggggc cggaacccat tc 802

<210> 153
 <211> 461
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (77)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (437)
 <223> n equals a,t,g, or c

<400> 153
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 agtctgttcc ccgcccgcga gatgatgaac aatggcctcc tccaacagcc ctctgccttg 180
 atgttgctcc cctgccgccc agttcttact tctgtggccc ttaatgccaa ctttgtgtcc 240
 tgggaagagtc gtaccaagta caccattaca ccagtgaaga tgaggaagtc tgggggcccga 300

gaccacacag	gtgggaacaa	ggacaggggg	atttaagcag	tcaaaaggaa	aaacatgtta	360
agaccctaga	cttgatatatt	gacacacttg	taccttgtaa	ggcagaggaa	tgtaattaaa	420
aagcacttat	ttggcwnaaa	aaaaaaaaaa	aaaaaaaaaa	c		461

<210> 154
 <211> 2388
 <212> DNA
 <213> Homo sapiens

<400> 154						
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aaccgaggcc	ggcgcttcaa	gtgggccatt	gagctaagcg	ggcctggagg	aggcagcagg	180
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aagcaagtgc	ctgataccag	cgtgcaagag	acagaccgga	tcctggtgga	gaagcgctgc	300
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gcaggcaata	ctatctccat	cttccttact	atgatggtgt	gtatgatggc	ctggcgaccc	420
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<210> 155
 <211> 642
 <212> DNA
 <213> Homo sapiens

<400> 155
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 cacaagatta cactgaacat attagctact aaaaaggcac tgctaagaca ttcaagcaaa 120
 tagctattac acactactgc agattttaca ggttttcta tctaacatat gtttgaaaaa 180
 tccgtgagta ttccaaaata tatttaataa tggaaatctc gcattaatat accatccatg 240
 tgtttttacc atttgccctta atattgaata tactgtttac ctcacactaa aaagaaaacc 300
 agaagcctta tttgtgattt tgggagtggga agcttccatt tttgtgtcaa aaatgaatcc 360
 tgattcttat ggaaatctct gttattaaga tatttcaaga tgagacaaca ctgaagatca 420
 aattgtgttt agtatcacta tcttctctcc tcgtttctct cttactcctc atcctcccag 480
 aatctaccag tttatggtag aaagatggga acctattttg aatgtgtttt tttttttcca 540
 tgatgtccaa ttttgtgtg ggaaaggatt tggataaaat ttttgtttaa attttggtag 600
 atttttatct atacaaattt aaataaaatt atgttttcta ag 642

<210> 156
 <211> 1251
 <212> DNA
 <213> Homo sapiens

<400> 156
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 agagaaaata tcacgggccc ctttcacaa tgcagttgct gtagtcatct acaataataa 180
 atccaaagag gagccagtta ccatgactca tccaggcact gagcatatta ttgctgtcat 240
 gataacagaa ttgaggggta aggatatttt gagttatctg gagaaaaaca tctctgtaca 300
 aatgacaata gctgttgga ctcgaatgcc accgaagaac ttcagccgtg gctctctagt 360
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 gaatttgcca tgtactgata acgtagcatt cgatatggaa aggctcacca gaaccaagc 780
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<210> 157
 <211> 2127
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (312)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1212)
 <223> n equals a,t,g, or c

100

<400> 157

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gacaaccagt	caccagcctc	aggacagata	caaagctgtc	tggcttatct	tcttcagtct	180
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ggcgtcagcg	cncctgcag	cacccttgcc	tgagcggaac	tctctcagt	ccatcttcaa	360
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gtttggtctg	gctggccttc	tgctgcccag	ctracacggc	ccccatcatg	agtggccagg	660
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<210> 158

<211> 1625

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1066)

<223> n equals a,t,g, or c

<400> 158

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cagatgaagt	gtaaatggat	aatcttttaa	tggatctaaa	cctagaaagt	ttcacttact	360
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<210> 159

<211> 1687

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (334)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (505)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1044)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1670)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1678)

<223> n equals a,t,g, or c

<220>

<221> SITE
 <222> (1683)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1684)
 <223> n equals a,t,g, or c

<400> 159
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 ctaaggggacc aaaagcgtat gcgacttact gaagtgcagg atgataaaga ggaggaggag 240
 gaggagaatc cactgctggt accactggag gaaaaggcag tactgcagga agaacaagcc 300
 aacctgtggt tctcaaaggg cagctttgct gggnatcgag gacgatgccg atgaaggccc 360
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 gtctacacct ggacgtgtgg gccacttaag ccctccccac ccccatccta ttcctraata 1620
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 cannttt 1687

<210> 160
 <211> 1842
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (19)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (62)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (1793)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1834)

<223> n equals a,t,g, or c

<400> 160

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gaaacaagaa	gaaaaaaacc	attggttcac	caaaaaggat	tcagagtcct	ttgaataaca	240
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gacctccagc	acccaatcta	gctggagctg	ttgaattcaa	tgatgtgaag	accttgctca	480
gagaatggat	aactacaatt	tcagatccaa	tggagaaga	cattctccaa	gttgtgaaat	540
actgtactga	tctaatagaa	gaaaaagatt	tggaaaaact	ggatctagtt	ataaaataca	600
tgaaaagggt	tcgtagcaaa	tcgggtggaat	cggtttggaa	tatggcattt	gactttattc	660
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tattaccaga	gagcctgatg	ctctctgata	gctgtgccat	aagtgttgt	gaggtatttg	780
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aaacaggatc	aaggattaat	ggtataaaaa	tctctactgg	ttaccgggtg	gcngggccat	1800
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<210> 161

<211> 770

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (744)

<223> n equals a,t,g, or c

<400> 161

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gtgtcttctg	tcattgttgt	aagtttctct	aggcctcccc	agctatgtag	aactgtgagc	180
caattaaacc	tcttttctct	ataaattatc	cagtcctata	tatttcttca	tagcagtgtg	240
agaacagata	ataccgtaaa	ttggtatcac	agagagtggg	gtgttgctat	aaacacatct	300

gaaaatgtta	aagcaaattt	ggaactgggt	aacaggcaaa	ggctggaaca	gttkgaagaa	360
cagttaagaa	gaagacagga	aaatatgaga	aatcttgaaa	cttcctagag	tcttaaaggt	420
ctcagaagac	atgaagatgt	gggaagcttt	ggaacttcct	agagacttgt	ttgaatggct	480
ttgacaaaaa	tgctgatagt	gatatggaca	atgaagtcca	ggctgagctt	atccagacag	540
acataagaag	ctcgctggga	acttgagtaa	agatcactct	tgctaggcaa	agagactggg	600
ggcctttttt	cctctgccct	agagatctgt	ggaaatctga	acctgagaga	gatgatttag	660
ggtatctggc	agaagaaata	tctaagcggc	aaaaccttcm	agagggaagca	gagcataaac	720
gtttgaaaaa	tttgagcct	gacnatggga	gaccaaagtt	aaaccaatt		770

<210> 162

<211> 519

<212> DNA

<213> Homo sapiens

<400> 162

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ccgtgtgaca	aggtgtcctc	tctgagcctc	agtcacacac	tgcttaacg	gttgggcctc	180
atggagctgt	ttgtgaaggt	taaatgggaa	gacataaagc	acttagccca	gagccaagga	240
catgctgaat	aggataatgg	tggcctcctt	tggcgctgtg	ctgggtgcagg	tgtgccgagg	300
aaytgggcag	gggtgacaga	tacctcttct	aacctagtct	ctttccaaga	acctaatggg	360
tgtctctccc	tccccaggc	aattggaagg	aggaggctgg	gccccagccc	cagaatacgg	420
gaggtttctc	accgtggtag	ggaaattgct	gggttggggg	tgtgggcaac	cacagtgatc	480
gtctctctgc	aggacggatg	aggctttgct	gacagaggc			519

<210> 163

<211> 753

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (720)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (730)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (736)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (741)

<223> n equals a,t,g, or c

<400> 163

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tgtttaaate	ttttcagtg	cttccctttg	tacttagaaa	aaaatgcaac	ttcttctgct	180
gggactcatc	cgctcacagc	cttccccctc	accctctctc	tgctcatg	tctgccccctg	240
cctgccatgc	ctccgatact	caccttttgt	accccagcac	ccgtgccctc	tgccccctga	300

105

tctttgcttg	gctggttgc	cctcactcag	tgttcaggac	aaatgctcct	ggccctaccc	360
catctagcca	gtctagccc	gtcttccttg	tcttcctgt	ttcattcatg	gctcttattg	420
tttggtwact	tggtgctgt	tgacttttaa	ctctctcagt	ccccactgga	atgcaagcga	480
tctcccaagc	tcctagaatt	gttcctgcct	cttcacaggc	ccttacgctg	tggtgctcg	540
tgccgaattc	ggcacgaggg	tatgtgcact	tgctggtatg	tatgtagggtg	tttgctaaca	600
catacgtgca	cacgcagaat	gcttcagggtg	gactgcacag	cctctagttc	gcagcccca	660
cccctccctt	tgscctgca	ctctccctc	tctgagctgc	attcgcata	aagggtgcan	720
ggttcctgan	ccgcgnagcg	ncacctcctg	gga			753

<210> 164

<211> 1893

<212> DNA

<213> Homo sapiens

<400> 164

tgcagttttt	ttttttttt	tttttttkt	aatttaaaca	aataccaaaa	gctttattta	60
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ttctgcaaac	agtgtagtaa	gaaaggtaat	ttgagaattt	ccaaagatgt	tctcgctagc	180
cattatttat	ggtaattaca	taacattttg	atgtcaagtt	attacagact	taaaagttaa	240
tatagcataa	ttttacaatc	gtactttcac	tatgattttt	attttaaccc	tggatattat	300
tggtttgaag	ctaataattat	cagtcctatt	ggctgtcact	gtcacagatc	tgaagatatg	360
tttaaatcca	tcaagctagg	aagatatcaa	aataattaaca	atcttcaagt	atagtgagaa	420
aaaaactgat	ttaagtgtta	gcatttctaa	acttgagact	ctaacagtaa	aaacaaagta	480
atctgaaacc	tgtttccatg	ggtaaaacac	tctgcctggt	attcttgtac	acaaaattta	540
ctaaatatgt	gaatatcata	aaatgaaaat	atcactccct	tcaatttctt	tggccttcac	600
aaattcaatg	tgactatgat	ccttttcaat	aataacttyca	atgacattgt	gcttcttttag	660
aaaaatcact	taagttgtag	catacaatag	ttaacattag	ttcttttatt	gctatggtat	720
atgctaattt	ttttaaaagg	ggaaaaaaa	acccagagaa	cttattaaaa	tgtttggttaa	780
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ccatcctcag	aactaactca	agacaagaga	tctgtattca	aaaagataaa	acaatctcat	960
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aaatgggata	gagagtaaga	agacaggaga	gagaggagaa	accatgtttt	ttcggacgcg	1860
tgggtcgacc	cacgcgtccg	cggacgcgtg	ggc			1893

<210> 165

<211> 2153

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (101)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1670)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2134)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2135)

<223> n equals a,t,g, or c

<400> 165

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cagggtctcaa	gggctgtggt	cgctcaggg	tctcatttcc	ccaggccaag	ttcaaggcag	180
cagccctttg	tgaggcgctc	ttggccctgg	gctggaggga	gaactttaag	cttttttgct	240
cacagggacg	tggtatgggc	cctgggtgca	gggtgccaca	ttctgcta	gagagctttg	300
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tatgtcaaaa	ataaagccgc	tagaaacgga	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	2100
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<210> 166

<211> 1251

<212> DNA

<213> Homo sapiens

<400> 166

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atcttcgccc	tcgtctgggt	cctccactac	cgagaggggc	ttggctggga	tgggagcgca	180
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aattggaaag	gatgtgatta	atataaataa	tagcagatat	aaattgtggg	tatgttacct	1140
ttatcttggt	gaggaccaca	acattagcac	ggtgccttgt	gcakaataga	tactcaatat	1200
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<210> 167

<211> 882

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (522)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (752)

<223> n equals a,t,g, or c

<400> 167

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cgcgcactga	cttcaacaat	tctggcgccg	ctacgggaag	tctccccac	ctcatgaaat	840
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<210> 168
 <211> 1208
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (161)
 <223> n equals a,t,g, or c

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gaatatagat gaagctgggc tcatttctat tttccaagtk nytggggggcc atagtgattt      180
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 <212> DNA
 <213> Homo sapiens

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<210> 170

<211> 1624

<212> DNA

<213> Homo sapiens

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<211> 2003

<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1999)

<223> n equals a,t,g, or c

<400> 171

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<210> 172

<211> 786

<212> DNA

<213> Homo sapiens

<400> 172

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<210> 173
 <211> 1758
 <212> DNA
 <213> Homo sapiens

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 aaaaaaaaaa aaactcga 1758

<210> 174
 <211> 1369
 <212> DNA
 <213> Homo sapiens

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<210> 175

<211> 2379

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1881)

<223> n equals a,t,g, or c

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<210> 176

<211> 1348

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (407)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (408)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1331)

<223> n equals a,t,g, or c

<400> 176

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gcctgggaca	gtgccaggca	ccccaggacc	ccttccaggc	ttgtctcctg	ctccaccgcc	360
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<210> 177
 <211> 1502
 <212> DNA
 <213> Homo sapiens

<220>
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 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (470)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1024)
 <223> n equals a,t,g, or c

<400> 177
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 gaaactcttc tatagagaat ggagttggat taataatagg tgatttttta cactggactg 180
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 cgtctcactc tgaaagcagc aggagatggt gtttactttg tttctatccc ctttgtctgg 300
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 accgatgctt actttttttt tttttnacta cttgttttat tccttccagn aaagtatagc 480
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 ga 1502

<210> 178
 <211> 1637
 <212> DNA
 <213> Homo sapiens

<400> 178
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 gggatatcaag tcaagatata aagactgcag catggcagcc ctgacatccc atctacaaa 180

cctgaggaag	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	240
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gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	360
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gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	1560
gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	gctgaaagt	1620
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<210> 179

<211> 2911

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (622)

<223> n equals a,t,g, or c

<400> 179

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aaaacagtgg	aatggaaaaa	cagtgtctgt	gtcatcctgt	aatatgctcc	ttgtcaacaa	240
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<210> 180

<211> 519

<212> DNA

<213> Homo sapiens

<400> 180

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gtgcccacc	ttcagaccct	ggcagtcctc	actgaggcca	ttggcccaga	gcccgccatc	180
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<210> 181

<211> 968

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> n equals a,t,g, or c

<220>
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 <222> (45)
 <223> n equals a,t,g, or c

<220>
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 agttcctgag ggcctggggc agcccctggg ggagagacta gaaaacacag aaggaagcag 900
 cacagggaga cccgctttgt gatctgcatg tgtgacactg attctttgga aataaagagt 960
 ggaagctg 968

<210> 182
 <211> 1128
 <212> DNA
 <213> Homo sapiens

<400> 182
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 aggggtatat tagaaaaatc atcctcataa tcattctggg aagtttttcc tccccaaaaa 180
 aagccatcct gatgggtttt caaaaccaga aaaaagctct taatgaggaa cagaccactg 240
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 agcamagatt agccatactg agatttggtt aaatcattct gtctaagcaa tggagggtgt 480
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<210> 183

<211> 2276

<212> DNA

<213> Homo sapiens

<400> 183

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ttgacttttt	atatgatatt	gtgcaaatgt	ttgccatagg	caattggtag	ttaaatagaa	960
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<210> 184

<211> 3374

<212> DNA

<213> Homo sapiens

<400> 184

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aaaccccgag	caaatattat	tcctacagta	aagaaaatag	ttctgcttgc	aggatgggca	360
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ccttatgaag	tattaaat	ggatcctgga	gccacagtag	cagaaattaa	aaaacaatat	480
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ccgggggggg	cccc					3374

<210> 185

<211> 1337

<212> DNA

<213> Homo sapiens

<220>

120

<221> SITE

<222> (1337)

<223> n equals a,t,g, or c

<400> 185

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gccagcgtgg	cgggcctggc	ggctcccggg	tggtgagaga	gcggtcgggg	aacgatgaag	180
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taatgctaatt	tatttttgct	gatgtcatat	gttaaagagc	tataaattcc	aacaaccaac	1140
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aaaagaagcc	aaatttatta	ctttgtgttg	gggtttttta	aatattaaga	aatgtctaag	1260
ttattgtttg	caaaaacaata	aatatgattt	taaattctct	taaaaaaaaa	aaaaaaaaacc	1320
ccgggggggg	gcccgggn					1337

<210> 186

<211> 941

<212> DNA

<213> Homo sapiens

<400> 186

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aggaccccca	gctccgacat	gtcgccctct	ggtcgcctgt	gtcttctcac	catcgttggc	120
ctgattctcc	ccaccagagg	acagacgttg	aaagatacca	cgtccagttc	ttcagcagac	180
tcaactatca	tggaacttca	ggccccgaca	cgagccccag	atgcagtcta	cacagaactc	240
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<210> 187

<211> 678

<212> DNA

<213> Homo sapiens

<400> 187

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aaagaggagg	atgtttaaat	gcctccagac	tacattcctt	tttattcttg	attttacctg	180
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acaaaaatta	gccgggcatg	gtggcaggca	cctgtaatcc	tagctagtgtg	ggaggctgag	540
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cactccagcc	tgggtgacag	ggtgagactc	tgtctcaaaa	aaaaaaataa	ataaataaag	660
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<210> 188

<211> 1848

<212> DNA

<213> Homo sapiens

<400> 188

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ccgccggccc	ggccgagcgc	ggcgcccgct	gcgattgcag	tcgcggcggc	ggaggaagag	180
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gcaaaaggta	atthttccacc	tcaaaagaag	ccagtttggg	tggatgaaga	agatgaagat	420
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gaaagtaaac	tttcgaaaga	caaccttaaa	aagagactta	aagaagaatt	ccaacatgcc	540
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<210> 189

<211> 1292

<212> DNA

<213> Homo sapiens

<400> 189

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<210> 190

<211> 906

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (144)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (145)

<223> n equals a,t,g, or c

<400> 190

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actcga

906

<210> 191
 <211> 1941
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (561)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1414)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1422)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1427)
 <223> n equals a,t,g, or c

<400> 191
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<210> 192

<211> 2118

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (13)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1324)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1643)

<223> n equals a,t,g, or c

<400> 192

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125

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<210> 193
 <211> 1538
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (112)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (147)
 <223> n equals a,t,g, or c

<400> 193						
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 <213> Homo sapiens

<220>
 <221> SITE

126

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<220>
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 <223> n equals a,t,g, or c

<220>
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 <223> n equals a,t,g, or c

<220>
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 <222> (438)
 <223> n equals a,t,g, or c

<400> 194

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<210> 195
 <211> 1001
 <212> DNA
 <213> Homo sapiens

<400> 195

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127

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gcccttcccc	aaccactget	ccacccgtgg	taaccacat	tctattctca	acttcctggg	960
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<210> 196

<211> 1458

<212> DNA

<213> Homo sapiens

<400> 196

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tgtggaaggt	ggctcatcaga	tagtagacat	tttctaggat	ttattttctac	ctgcatatgt	180
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<210> 197

<211> 1282

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (675)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1195)

<223> n equals a,t,g, or c

<400> 197

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gtattttcat	catttcttgt	ctcttcggaa	gctaacacca	tgctataata	ggcactaaat	720
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<210> 198

<211> 951

<212> DNA

<213> Homo sapiens

<400> 198

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<210> 199

<211> 1740

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1310)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1736)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1737)

<223> n equals a,t,g, or c

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<210> 200

<211> 1707

<212> DNA

<213> Homo sapiens

<400> 200

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130

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<210> 201

<211> 779

<212> DNA

<213> Homo sapiens

<400> 201

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<210> 202

<211> 1617

<212> DNA

<213> Homo sapiens

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<211> 1974

<212> DNA

<213> Homo sapiens

<400> 203

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132

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<222> (340)

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<212> DNA

<213> Homo sapiens

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<210> 207

<211> 1480

<212> DNA

<213> Homo sapiens

<400> 207

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gctggctgaa	cgagagcagg	aagaagccat	tgctcagttc	ccatatgtgg	aattcacccg	240
gagagatagc	atcacctgtc	tcacgtgcc	ggggacaggc	tacattccaa	cagagcaagt	300
aaatgagttg	gtggctttga	tcacacacag	tgatcagaga	ttgcgccctc	agcgaactaa	360
gcaatatgtc	ctcctgtcca	tcctgctttg	tctcctggca	tctggtttgg	tggttttctt	420
cctgtttccg	cattcagtc	ttgtggatga	tgacggcatc	aaagtgggtga	aagtcacatt	480
taataagcaa	gactcccttg	taattctcac	catcatggcc	accctgaaaa	tcagggaactc	540
caacttctac	acggtggcag	tgaccagcct	gtccagccag	attcagtaca	tgaacacagt	600
ggtgaatttt	accgggaagg	cagagatggg	aggaccgttt	tcctatgtgt	acttcttctg	660
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ggcttttttt	tttttttagaa	agttagaatt	gtttttacca	agagtctatg	tggggcttga	1380
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<210> 208

<211> 872

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (422)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (847)

<223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (856)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (872)
 <223> n equals a,t,g, or c

<400> 208
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 ctccctagta gctagtgtct tctaagtttt tattttaatta gaacaactcc atttccattt 180
 caaggtaggt caatgggggg aaaagcctca tgatttaaac tgaagttaac aacacagctt 240
 ttaaaatgaa aactcatact ccaacttcta aagtatattt gagctgattt gtttccaaaa 300
 caaagatatg ctgtacctaa aactgctaaa acaaaaatat aaagacaagg actaggtgat 360
 taaggggaga gaaaaatcat ytcttttcca ggaaaccttt gctaaaataa gcaaaacttg 420
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 tgaacttcaa tggggatttg tcacctaggt ctccatctat aggaatacct tcacatacct 600
 atctattcat gcacatattc tgaaaacagg tacatacaaa attacaacaa aggaaaaaaa 660
 ttctattgaa cacttaaaaa tagaaacagg ccaggcacgg tggctcatgc tgtaatccca 720
 acaatttggg aggctgaggg tgggtgatca cctgaggtca ggagtgtgag accagcttgg 780
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 acactcntac aatccnggct gactcgggaa an 872

<210> 209
 <211> 1779
 <212> DNA
 <213> Homo sapiens

<400> 209
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 ttggcttcac wtgggtcttg agataaaatg gccagcataa atgctgttta tattcacgtt 180
 ttccctagggtg tgtgtgtgca ggccacagca gcattgccctt ggtgtagtca gtgccgaaas 240
 ggggtctgttc cttcttgagc ctgcctgcag ggatgggtctc cttttaaaagc aggttgtgtg 300
 cagcattcag tacactgaag gtaagctaaa ccatcaacat ctctgggtgtt ttaagatgtt 360
 attttattgg aacaactgac aaatgagggg tgttagcttt gtggcagaat tccctgcatg 420
 tgtgataact gatcttgttt tatttttttg cattgcaact gtggcatagt tacaatttct 480
 gtttgktcat cacattttaa attggragag aacgcgcttg akggatagag cgccttcagk 540
 gtactgtttc ttattaactt tacttttttt aaatcaactt gctatagact ttatatacat 600
 tttgttaaat atagttccta gtgacataga aacgatgcgt agttttcatt tactaattac 660
 aaatggttag gcctaattct gaaagtcctc atattttaaag gctagacaac gtaatgaaat 720
 ttttaactat ttgtatgtca ttttgaaagt gtactgcttt atggtaaaag tgtttttcat 780
 ttgttcattg ttttcattat ttgtgatcat gttgtctttc aatacaggca taaaccttcc 840
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 tttgtaaatg aagcttttct ttaagaatgt gacttttaaag tgttgtctat tgcataaaac 960
 agttgacact cacttattgt aaagtgaaga ttgttctact gcatgtgaag tggaccatgc 1020
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 aaaatcctac aaatattgtc agctttcagt gtagtgaat tattcctgta ggttatggg 1320
 tataattcag gatttaacta atgtttctgc tatttttctc cttttccttt tgatgggtgcg 1380

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ttggtgcatt	caagaatgga	aaatcagaat	agcagcattg	attcttctgg	tcgagctcag	1560
tggaagatga	tgacaaccag	aagacatgag	ctaagggtaa	gggactgttc	tgaagaacct	1620
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ttatttatgg	taccatttga	attgtaactt	gcatttttagc	agtgcagtgt	tctaattgac	1740
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<210> 210

<211> 2110

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (750)

<223> n equals a,t,g, or c

<400> 210

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gtcctgtccc	gacgccttgg	aaagcgggtcc	ctcctgggag	cccgggtgtt	gggaccaggt	180
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ggtacggggg	tcaagagtgc	acaggactgg	tggwgagca	cagctggatg	gagggtcagg	420
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tgtttttggt	tctcccaaaa	ctgatcatgg	ctttgagacc	gatcctgacc	ctttcctgct	900
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gccaaactgt	ggcaaagttc	tgcgtccat	tgtgggcatc	aaacgacacg	tcaaagccct	1020
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aaaagaagga	acagctcggt	ctgcttcctg	ctgagtcggt	gaattctttg	ctttctaaac	2040
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aaaaactcga						2110

137

<210> 211
 <211> 938
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (200)
 <223> n equals a,t,g, or c

<400> 211
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 ttttcttgat gtttgaaaaa agtttaagct atgtccta attaaaatga gcacaaacta 120
 cttacagat gtctgttccc tcttctctta cttaaattat ctttattttc accatcacct 180
 cccagtgcg aacacctgan ctctgtgttt tgtggttgga tcctgggttg ccaagttcct 240
 atttggtcag tccctggcct gtggggcggc ctcaggaagt ggcagtctct tcamgragga 300
 tcgttcatyt ccagtataac cawtttgta ataatagttg ataattccca gcttttacca 360
 gatgartttt gacttatttt tcctcctttg acctgttcaa agctaacata tctcggtcag 420
 ttcggagagg gtgggggatt tgagaatgtg aggaggagt ggggttagaat gggtttgcc 480
 atctgggcaa ggaaagagtt ctagtcgat tgggcacaat gacaaaatga ttccatggat 540
 agaatcgtcc catgttgctg gaacacctca cgtgttgta acgccttaaa ttcttgccat 600
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 actgcatctg tgtcatccc tgcaccttct tgcagaaagc cgccccctca ggccaagatg 840
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 tctttaaaga ttctctccca acattcagtc gtgctcga 938

<210> 212
 <211> 1551
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (420)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1017)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1408)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1423)
 <223> n equals a,t,g, or c

<400> 212
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 ttttttttgt tttgtttttt ctctatttgg cactttctag ggattgggtct ataaattttt 180

tgaaagatca	taggataaat	ttctttgtag	caacttccta	ttttagtgtt	tatgttaggg	240
garcccccarg	tgtccctgct	gatacgccat	tagggccact	tctcagcctc	tggctacatc	300
ataatgctttt	tttttctatc	ttgccaaagt	ttccmgaaaa	ttkakgtttt	ctaatttttaa	360
aaaaattggg	tgtggagatg	ggatgggacc	tctttataag	ccctgaaaat	aagtgatttn	420
ttttaagtgc	tattctgcta	taaacctgat	tctcactttt	ttctgtagac	aacagttttt	480
tataatatat	ctattttgtg	tggacattat	ttccttttaa	ccaatactga	aattccatag	540
tgtawacttt	ctccacattt	tctttgatta	atacttyctt	aaaatagaca	cttggattgg	600
caccagctgt	caccaataaa	gctgccctga	acattgtcaa	tcaatcctgt	taaccaattt	660
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atgtccccac	cattttcttc	tgtttcatag	ttttgccttg	tatgtttaat	cctttaaggc	1260
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ttttcttcag	ccctcaggat	gaattccaca	attttacaca	tagcaccagt	taaggaatag	1500
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<210> 213

<211> 997

<212> DNA

<213> Homo sapiens

<400> 213

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tagcccaagc	taagtcaggt	ggaaaggcag	aaatatattt	agaagartca	tttctacaaa	180
aacagagttg	ttctaaatga	aatggccaga	tatttcatct	tcttcatact	agtattttatg	240
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aaaagcaa	gatttgagga	acaaaagagt	ggacacagag	cctctcagaa	gatggctcca	360
tcttctgaga	tgatcttctg	agatcatcaa	ttttctgcac	ctgatgtcct	actccaattg	420
tagtagataa	gagcaaagac	acttctgat	cctgtggaaa	atgctggagc	cctgctgatg	480
gagaggctga	cactgggacc	aacagaaggc	cggacattta	tttgctgcag	cccttctgca	540
cctgggccct	cttcaggcct	tgtaccttgc	actccccatg	ccactgtagc	acctggtaag	600
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ggaaaccact	aaattccact	tgacaaacca	gtttgttcag	ttttgacttt	tgcaaatttg	720
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atgtcagtg	catgcaggca	agtacagata	tggaaatgaa	agctctgtct	acaactgcaa	960
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<210> 214

<211> 1496

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (450)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (451)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (454)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1485)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1492)

<223> n equals a,t,g, or c

<400> 214

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tgatgattga	ttttagggtt	acaatacat	tttagcaagt	aagtgaattt	ggcattacga	660
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cgggcggggt	cgggctccca	gagagggtt	cagggacgcc	agcccggagg	catcgggccg	840
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cgctgcttca	gaagtcgggg	cggcagttcg	agccttgtaa	gtttttttca	gccctggccc	1440
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<210> 215

<211> 1308

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1241)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1247)

<223> n equals a,t,g, or c

<400> 215

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gccataaccc	ttttttactt	ccattaggcc	gtataactgg	ngggacngct	ggtcggtata	1260
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<210> 216

<211> 1705

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1281)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1704)

<223> n equals a,t,g, or c

<400> 216

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cacggaagat	ccgttcagtg	tccatcgctc	tgaaactctt	ttcaacatct	ccaggttctt	780
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<210> 217

<211> 999

<212> DNA

<213> Homo sapiens

<400> 217

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tcagacagka	gtcccgataa	gcagatcacc	agtcctccac	tgctcttctc	gtcggccttg	180
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attgagtgyc	tttaataatag	tytacaata	ctatgtattt	atgcaaaact	gttaaagttc	300
tcactctgta	tgattggata	cttggctctg	tcagtagtgg	tcagcattgg	gttgtgagct	360
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<210> 218

<211> 941

<212> DNA

<213> Homo sapiens

<400> 218

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gagaatgaca	gctctggttt	ggagaaaagg	gccggatggg	ggctctagaa	agcccatcct	300
tctgctcttc	ttttttctcc	cccttatatt	gtgctttcat	tcattcattc	attcatcaaa	360
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<210> 219

<211> 575

<212> DNA

<213> Homo sapiens

<400> 219

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cagttctggg	gccggcagtg	ctgggccctt	tagctccttg	gcacttccaa	gctggcatct	480
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<210> 220

<211> 3018

<212> DNA

<213> Homo sapiens

<400> 220

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catcatttat	gatataatga	atgaattaat	gggaaagaga	ttttctccaa	aggaccggga	180
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tgctaccaa	gtacatggcc	ttttaaaaac	cggagacaac	tggaaattca	ttggacctga	300
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<210> 221

<211> 2031

<212> DNA

<213> Homo sapiens

<400> 221

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144

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<210> 222
 <211> 968
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (241)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (954)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (961)
 <223> n equals a,t,g, or c

<400> 222						
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catttgcata	cggaaaggaa	ggctatgcag	aaggcaagat	tccaccggat	gctacattga	480
tttttgagat	tgaactttat	gctgtgacca	aaggaccacg	gagcattgag	acattttaac	540
aaatagacat	ggacaatgac	aggcagctct	ctaaagccga	gataaacctc	tacttgcaaa	600
gggaatttga	aaaagatgag	aagccacgtg	acaagtcata	tcaggatgca	gttttagaag	660
atatttttaa	gaagaatgac	catgatgggtg	atggcttcac	ttctccaag	gaatacaatg	720

145

tataccaaca	cgatgaacta	tagcatat	gtattttctac	tttttttttt	tagctattta	780
ctgtacttta	tgtatwaaac	aaagtcmtt	ttctccmagt	tgkatttgct	atttttcccc	840
tatgagaaga	tattttgatc	tccccaatac	attgattttg	gtataataaa	tgtgaggctg	900
ttttgcaaac	ttaaaaaaaaa	atttaaaaaa	actggagggg	ggcccgtacc	caantcgccg	960
natatgat						968

<210> 223

<211> 1404

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1351)

<223> n equals a,t,g, or c

<400> 223

cgttttccgg	ccgtgcgttt	gtggccgtcc	ggcctccctg	acatgcagcc	ctctggaccc	60
cgaggttgga	ccctactgtg	acacacctac	catgcgga	ctcttcaacc	tcctctggct	120
tgccctggcc	tgagccctg	ttcacactac	cctgtcaaag	tcagatgcca	aaaaagccgc	180
ctcaaagacg	ctgctggaga	agagtcagtt	ttcagataag	ccggtgcaag	accgggggtt	240
ggtggtgacg	gacctcaaa	ctgagagtgt	ggttcttgag	catcgcagct	actgctcggc	300
aaaggcccg	gacagacact	ttgctgggga	tgtactgggc	tatgtcactc	catggaacag	360
ccatggctac	gatgtcacca	aggtctttgg	gagcaagttc	acacagatct	caccctctctg	420
gctgcagctg	aagagacgtg	gccgtgagat	gtttgaggtc	acgggcctcc	acgacgtgga	480
ccaaggggtg	atgcgagctg	tcaggaagca	tgccaagggc	ctgcacatag	tgccctcggt	540
cctgttttag	gactggactt	acgatgattt	ccggaacgtc	ttagacagt	aggatgagat	600
agaggagctg	agcaagaccg	tggtccaggt	ggcaaagaac	cagcatttcg	atggcttcgt	660
ggtggaggtc	tggaaccagc	tgctaagcca	gaagcgcgtg	ggcctcatcc	acatgctcac	720
ccacttgccc	gaggctctgc	accaggcccg	gctgctggcc	ctcctggtea	tcccgccctg	780
catcaccccc	gggaccgacc	agctgggcat	gttcacgcac	aaggagtttg	agcagctggc	840
ccccgtgctg	gatggtttca	gcctcatgac	ctacgactac	tctacagcgc	atcagcctgg	900
ccctaatagca	cccctgtcct	gggttcgagc	ctgcgtccag	gtcctggacc	cgaagtccaa	960
gtggcggaagc	aaaatcctcc	tggggctcaa	cttctatgg	atggactacg	cgacctccaa	1020
ggatgcccgt	gagcctgttg	tcggggccag	gtacatccag	acactgaagg	accacaggcc	1080
ccggatgggt	tgggacagcc	aggyctcaga	gcacttcttc	gagtacaaga	agagccgcag	1140
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gacctgtct	aggtgggcat	tgcggcctcc	gcggtggacg	tgttcttttc	taagccatgg	1320
agtgagttag	caggtgtgaa	atacaggcct	ncactccgtt	tgctgtgaaa	aaaaaaaaaa	1380
aaaaaaaaaa	aaaaaaaaaa	aaaa				1404

<210> 224

<211> 707

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (705)

<223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (706)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (707)
 <223> n equals a,t,g, or c

<400> 224

ngcgcgcctg	cagtcgacac	tagtggatcc	aaagaattcg	gcacgagggc	aggtccaggg	60
ctcagaaatc	agctctattg	acgaattctg	ccgcaagttc	cgctgggact	gcccgcctggc	120
catggagcgg	atcaaggagg	accggcccat	caccatcaag	gacgacaagg	gcaacctcaa	180
ccgctgcatc	gcagacgtgg	tctcgctctt	catcacggtc	atggacaagc	tgcgcctgga	240
gatccgcgcc	atggatgaga	tccagcccga	cctgcgagag	ctgatggaga	ccatgcaccg	300
catgagccac	ctcccacccg	actttgaggg	ccgccagacg	gtcagccagt	ggctgcagac	360
cctgagcggc	atgtcggcgt	cagatgagct	ggacgactca	caggtgcgtc	agatgctgtt	420
cgacctggag	tcagcctaca	acgccttcaa	ccgcttcctg	catgcctgag	ccccggggcac	480
tagcccttgc	acagaagggc	agagtctgag	gcgatggctc	ctggtccctc	gtccgccaca	540
caggccgtgg	tcattccacac	aactcactgt	ctgcagctgc	ctgtctggtg	tctgtctttg	600
gtgtcagaac	ttttggggccg	ggccccctccc	cacaataaag	atgctctccg	accttcaaaa	660
aaaaaaaaaa	aaaaactcrg	ggggggggccg	gtcccaatcc	ccccnnn		707

<210> 225
 <211> 1384
 <212> DNA
 <213> Homo sapiens

<400> 225

ggggaactgc	agtgcagca	ggagtaagag	tgggagggcag	gacagagctg	ggacacaggt	60
atggagaggg	ggttcagcga	gcctagagag	ggcagactat	caggggtgccg	gcggtgagaa	120
tccagggaga	ggagcggaaa	cagaagaggg	gcagaagacc	ggggcacttg	tgggttgagc	180
agccccctcag	ccatgttggg	agccaagcca	cactgggtac	caggtccctc	acacagtccc	240
gggctgccct	tggttctggt	gcttctggcc	ctggggggccg	ggtggggcca	ggaggggtca	300
gagcccgctc	tgctggaggg	ggagtgcctg	gtggtctgtg	agcctggccg	agctgctgca	360
ggggggggccg	ggggagcagc	cctgggagag	gcacccccctg	ggcgagtggc	atttgctgcg	420
gtccgaagcc	amcaccatga	gccagcaggg	gaaaccggca	atggcaccak	tggggccatc	480
tacttcgacc	aggtcctggt	gaacgagggc	ggtggctttg	accgggcctc	tggtccttc	540
gtagccccctg	tccgggggtg	ctacagcttc	cggttccatg	tgggtgaagg	gtacaaccgc	600
caaactgtcc	aggtgagcct	gatgctgaac	acgtggcctg	tcattctcagc	ctttgccaat	660
gatcctgacg	tgacccggga	ggcagccacc	agctctgtgc	tactgccctt	ggaccctggg	720
gaccgagtgt	ctctgcgcct	gcgtcggggg	aatctactgg	gtggttgga	atactcaagt	780
ttctctggct	tcctcatctt	ccctctctga	ggacccaagt	ytttcaagca	caagaatcca	840
gcccctgaca	actttcttct	gccccctctt	gccccagaaa	cagcagaggc	aggagagaga	900
ctccctctgg	ytcttatccc	acytctttgc	atgggammct	gtgccaaca	cccaagttta	960
agaraary	ararctgwgg	caggtatata	gagctggaag	tggacctgg	aaaacatgga	1020
taaccatgca	tcytcttgct	tggccacctc	ctgaaactgt	ccacctttga	agtttgaaact	1080
ttagtccctc	camactctga	ctgctgcctc	cttctctcca	gctctctcac	tgagttatyt	1140
tcactgtacc	tgttccagca	tatccccact	atctctcttt	ctctgatct	gtgctgtctt	1200
attctctctc	ttaggcttcc	tattacctgg	gattccatga	ttcattcctt	cagaccctct	1260
cctgccagta	tgctaaaccc	tccctctctc	tttcttatcc	cgctgtccca	ttggcccagc	1320
ctggatgaat	ctatcaataa	aacaactaga	gaatggtggt	caaaaaaaaa	aaaaaaaaaac	1380
tcga						1384

147

<210> 226
 <211> 774
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (773)
 <223> n equals a,t,g, or c

<400> 226
 tttaaagatg aagaaatgac aagggaggga gatgagatgg aaagggtgttt ggaagagata 60
 aggggtctra gaaagaaatt tagggctctg cattctaacc ataggcattc tcgggaccgt 120
 ccttatccca tttaattaat ttctctgaca attcaattat tttctgttat taatgttgcc 180
 actgctttct gtttgtctgc actttcttga taaatatttg ctatcgtttt actccagtca 240
 ttcgatgttg ctgagattta catatgactc ttgtcaacat ctcatctttt gacccaatct 300
 tattcattta ataagagggtc tcattcattt gcatggaaaa atgctcattg tatattgcaa 360
 agtgaataa acgagttgca aaacagtgtg tacatatatg tgtgtatata tgtacacttt 420
 atttgtacat ttctatgtga cataatgcaa aggaaagtgt ctgattttat tatacaccaa 480
 aggttaacag tgaatctctg tgtgatctct ttttttttct ttttgccctat ctgcatcttc 540
 tcacttgcca aaaaatgaat atatgtttat gtgtgtatat tacttgtgtc acaaaaaacc 600
 ctaaagtaga cagtaaaaga acttgtcaat cgccttttga aggcaatgaa acacttaata 660
 aactctcaat aacagaagcg taaaaatgaa atgtaaacct ccaattacct ctggatctct 720
 tagccagagt aataaactgg taattattac agataaaaaa aaaaaaaaaa aana 774

<210> 227
 <211> 865
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (344)
 <223> n equals a,t,g, or c

<400> 227
 ccacgcgtcc ggccttttctt ggccagaggg gcccgttgga ctcacggggcg gggcatgatg 60
 ggtaacagga ccggtgggggt ccccaggaag tcctagaggg ggtcgggggt tgggtggaca 120
 agcttttctc gtcctctccc gacagagctg acgtgtcctg gggtccaccg ggagcgggca 180
 tttccaccgg acgggaggggt tcgggggtgtc cggggctggg gaatacgtag ggggtgccc 240
 gcgggtgtggg gagttggggc gtgtggctgc agtcccggga gttcttgagg ggggtcggcc 300
 caccgagctt ccggaccggc tgatctgccc gtagcttgcc ggaggargg cggagctgac 360
 tctcgtctcc ttctcccatc cctccagtg gtgggtacgg gcacctcgct ggcgtctcc 420
 tccctcctgt ccctgctgct ctttgctggg atgcagatgt acagccgtca gctggcctcc 480
 accgagtggc tcaccatcca gggcggcctg cttgggtcgg gtctcttctg gttctcgtc 540
 actgccttca ataactctga gaactctgtc tttggcaaag gattccaagc aaagatcttc 600
 cctgagattc tctgtgcct cctgttggtc ctctttgcat ctggcctcat ccaccgagtc 660
 tgtgtcacca cctgcttcat cttctccatg gttgggtctgt actacatcaa caagatctcc 720
 tccacctgt accaggcagc agctccagtc ctcacaccag ccaaggtcac aggcaagagc 780
 aagaagagaa actgaccctg aatgttcaat aaagttgatt ctttgtaaaa aaaaaaaaaa 840
 aaaaaaaaaa aaaaaaaaaa aaaaaa 865

<210> 228
 <211> 1102
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (462)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (469)
 <223> n equals a,t,g, or c

<400> 228
 tttttttttt accattttaaa ataaaaatgaa agtgaccttc tgtttataaa aatctttgtc 60
 tgcattctctg cttatttcct tagaagagat tccaagaagc ggtgagtgat ttcacggcag 120
 cagagggttg ggacatatta cgggcgcgga tccctcttg agtgagatga ctctccggag 180
 agatttagtc gtcaccctcg cgtgtgagc tgcgtcacac cccagggatg tgtctatcaa 240
 gatggaagat cttttacacg ctcttgattt tgtttgscty tttttctatt actagtgaga 300
 akgaactttt ttatatgatt attatccatc ataatoaac acaaattact gcttcattgtt 360
 cttttacttt cctgtgaagg ttttagtgcc ttttaaaaaat tgctatatat taagcttggt 420
 aatacttcca tgctgtattt gtggscatca rtttccccgg gnacaggcnt gcacattttg 480
 ccttcacacg ctgggtggtt tttcattttc amttctattt ctggtcttc tatcgtttta 540
 tgttcagacg ggtttctccg tgtagaaagc agtttatgaa gatttacttt cgacagtctt 600
 ctctctactt tctacagtga attctctgat gtgtctggga gtttgggggt ctgggtaaga 660
 rtctctctct caccctattc tctattacga tccacagcct catgctttat garattggtg 720
 gccgggarcg ggggagattt gcggatcccc caagccagac tttatcccc tatccctgcc 780
 tctggatccc acgtacaggc ctgggaactc cctgtgggta gggccaatg gtctcgact 840
 ctcacctgta cccaggggct ggcacaggat ggtcaaggag agaggctgcc caagcgcac 900
 cytctggtgt cccctgaca cgcctccaaa gtgagcaggt aggtttcaac agccccacgt 960
 tgcagggtgg agatgaagct cagggtggag accagtatct cacagttctc tttgcatggc 1020
 cgggtacttg ttagtcaact gatcaagtga aaattctagc cccagaggca ggagaatccg 1080
 gaacaaaatt aaaccagcca gg 1102

<210> 229
 <211> 744
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (303)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (392)
 <223> n equals a,t,g, or c

<400> 229
 gaattcggca cgagagtggc tggagtctgg ctgcagaggg aagacatcag caggagggga 60
 gccagggcct gtcacatctt tcctctggcc attgtcctgg tctttgtaag cccagaatct 120
 ccccttcctt gaagggaggc cagcacccca ggagggcagc aggtgtgctg tgagggttgg 180
 agtagtgtga gaggtcaggg tacactagaa tggccatgga caccatgtgg ggggtgctctg 240
 ggctgggcca cagaacagtg tccttcctgc tgctcctccc ctgcagcttc ccccgacctt 300
 gtngtttatt tggtttgata ccaatcagca gaccctgcaa ggtggaagct cccaggctct 360
 cagtcccacs actctcatgt gccagtcacc cntactgtaa ctgccaatg agtacttctt 420
 gccactgcc aagatagagc cagtttacca agacagggga attgcagtag agaaagagtt 480
 gaatatacat agagccagct aaatgggaga gtggagtgtt cttattactt aaatcagcct 540

149

cccytaaaat	tcagaggtga	gaatttttca	aggacagttt	ggtggscagg	cctagggaaat	600
ggatgctgct	gattggctag	ggatgcaatc	ataggggtgt	agaaaagtgc	cttgtgcact	660
gagtcactt	ttgggtgagag	ctaccaagga	gctgctggtc	tgctggtccc	ggtagagcca	720
tctggtgtca	ggaatgcaaa	agtg				744

<210> 230
 <211> 1935
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1921)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1927)
 <223> n equals a,t,g, or c

<400> 230						
ntctacccta	atcaagatgg	ggacatactt	cgcgaccagg	ttcttcatga	acatatccag	60
agattgtcta	aagtagtgac	tgcaaatcac	agagctcttc	agataaccaga	ggtttatctt	120
cgagaagcac	catggccatc	tgcaaatca	gaaatcagga	caataagtgc	ttataaaacc	180
ccccgggaca	aagtgcagtg	catcctgaga	atgtgctcta	cgattatgaa	cctcctgagc	240
ctggccaatg	aggactctgt	ccctggagcg	gatgactttg	ttcctgtgtt	ggtgtttgtg	300
ttgataaagg	caaatccacc	ctgtttgctg	tctactgtgc	agtatatcag	tagcttttat	360
gctagctgtc	tgtctggaga	ggagtcctat	tggtggatgc	agttcacagc	agcagtagaa	420
ttcattaaaa	ccatcgatga	ccgaaagtga	ccaagaccaa	ggcccaccaa	ggcagcagac	480
tgtaaatcag	acaaacagat	ctctgagaag	gtgcatcagc	tgctttgaag	gctgaagatt	540
gttttgtatg	atactgcaca	gcatcaggca	ttttaaagca	gatctttact	aaacaggtta	600
atgagctaac	aagcagggtc	tctcgtcttt	gggctctttc	ctttctgagt	tgcatattct	660
attttcttgt	ccccaaagtag	agactagtac	tacaaaaagg	gaccacattt	ttcaagtatt	720
tctaagtata	aaaaacaaaa	caaaaatctc	ttaggaaatg	tctagacctc	cattcttgga	780
ttccctttct	ttccttttat	tttaaaaaag	aacagtaccc	ctcttttaag	atgctgtctt	840
acattaatga	gcatctaata	gaaagaaggt	atgagttgca	ctgaggatta	gaatagtggg	900
gcgttagtgg	cattatctat	aaatacactc	acctaaattg	aaagctaaga	aggaaatgta	960
aatataatat	atatttatat	ttgatgtaat	atggacatct	gcagattcta	ataaacaagg	1020
actattgctg	atagtaggct	gtgacatact	gtcttgtgaa	atggtttctt	tgacaaaatt	1080
taagctgagc	ttaaaagcaa	aaaaacaaaa	agtacacaga	aatattttat	aaaatgtaat	1140
acagtttatt	gaactttcta	ggtatggagt	ttgatggaca	gggctgccty	taatgagtgt	1200
gaaggtcact	aagtcactta	gacatctcac	cgtggaagtt	tgtgagcctg	cattaggaga	1260
tagactgatt	accatacatg	acataaaaag	gaacagtggg	tagctcatac	tttatgggtg	1320
ttcttctcct	ccgaaataat	atactgcaga	aatcccagac	agagctcctt	acaaaccttt	1380
aattgtaata	tatttttgat	gattattcac	attgaatgca	cagaccaaga	attcagtga	1440
tgtcattttt	taaaaaacta	atttgtattg	tctgctctag	tgatacaagt	tttactagt	1500
ataaactatt	ttaatcaacc	atactattct	tatggaaaaa	aatatctatt	ttggcaggtt	1560
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tgtatatcaa	taattaatca	ggaatgggtt	ttggtgcctg	aaaaattggc	catggaggca	1680
caccaaagct	tcaagcacia	gtcttgtaca	tggggccatca	ctgtctggtt	tcacttcgtg	1740
tgtttcttaa	acacatttag	ctgctttttt	aacaaactca	gccccatact	tgagtcctct	1800
gttgttgagg	gcatttccag	gcatctttta	agggaaactgt	gacaaacagc	ctcgggcaga	1860

150

tgaacacgga ggctctctgt tgtctgtctc tgagatcttt gtgtctggga atgcctaaag 1920
 nttttgnttt ttttt 1935

<210> 231
 <211> 1035
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1032)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1034)
 <223> n equals a,t,g, or c

<400> 231
 agaggcctgg ctgcgttgcc ctatctccgt ctccgccacc cacttagcgt tttaggcatc 60
 aattaccagc agtttctccg ccactatctg gaaaattacc cgattgctcc cggcagaata 120
 caagagcttg aagaacgccg cagttgcgtg gaagcctgca gagcaaggga agcagcgttt 180
 gatgccgaat atcagcgaaa tcctcacagg gtggacctcg atattttaac ctttacgata 240
 gctctgactg cctctgaagt tatcaaccct ctgatagaag aacttggttg cgataagttt 300
 atcaatagag aatagttagg tggtagacct acttcaagag aacctctgca ttccagtcac 360
 accaatcctg caacttgatt ttcagaagtc aagagtatat cgcgataaga cagtgcacag 420
 gtggagggga aaaaaagggg gagggggaag cttatcttga aaaaacatca cagaagtaga 480
 aaaaaatgtc gaaagcatta taactgtaac gttcttttag tttgtgattg atccacattt 540
 ttccccctgc attatggaaa atgtctctca gcattgcttt attacaaagt aaaggatggg 600
 tttataaaat tgagactgat gaaacatcaa tactagagcc catgaggatg aaagaaatta 660
 tcaaatagtg ctgaacagaa taagatgtta acgctgagtt attaggactg gaaggctatg 720
 aaaagaactt gaaattgtcg gaatatgtgc tctcttcacg tcatattcaa tagaagtttc 780
 tagtttaaga ttgattttgt gttttcttag gcatttcaag tgacaagcaa agtaaagtga 840
 tatattatgt gataaatcat gttttcaaga acgtcaaatt tctggacttt tttctttcaa 900
 tttttaatth tttaagtttt tttggtatta aaaaatcyat tcacaagcca aaaaatwtwt 960
 waaatwtwcm gcgaaaagcc aaaaaaaaaa aaaammaggg ggggccgggc cccatcccc 1020
 caaggggggtc cngnt 1035

<210> 232
 <211> 2218
 <212> DNA
 <213> Homo sapiens

<400> 232
 aggtattagg cccttttgtg ggagcccat gttttgtttt tctgagttgg tggggagggga 60
 sggaggggga gggctgaatt gttttgcaga ggaagatggc atctgtgctt taaatttctc 120
 attactgggt tagaaaacaa agagggaktg ccctgcacat tttcttttgt gctttttaa 180
 gtttcttaag ttggaacagg tttcctcggg cctgttttga ctgattgctg gagtgcattt 240
 gatagttaaa aattactaat tggttttatt tcccttcaca ctctgcctcc ccacttctcc 300
 ccccgttact gaaaaataac cattttagtg tcaggctaga aattgaattg ctgagttttg 360
 tgtatccttt aaattaaaaa ccacaagtgt ttattgtagt ggttaaactg tagcatctca 420
 gcatctgggt ggaagctgcc tatatttctt ccagttttaa ctggggacca tctgtgaaat 480
 taattttcca tccagacagc tgctgtgagc aaatgaacat aaatgctcgc tggaaattta 540
 ctaaccagtt tttatattga cctgcagtgt aaaaagcaca ttttaattata aacaatatat 600
 tcaaaatggg caaattttat tttcaaatgc agtgtagagc tagattaaaa gcaactcttt 660
 gccacctact ctgccctttt ggcaaaagta ccttgaacaa agaactctaa ggggtttatta 720

agaactcttt	attttcttca	taccctgttc	tctgcagtgc	tttctaacag	cttctgggtg	780
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agtcattggag	gactaaagcc	taagtccttt	tcacttttcc	tccatctgaa	ggtaggtgag	900
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<210> 233

<211> 2057

<212> DNA

<213> Homo sapiens

<400> 233

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gtttccctgg	cttaccgtga	tgacgcgttt	gctgagtggg	ctgaaatggc	ccatgaaaga	660
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152

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<210> 234

<211> 2084

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (775)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2080)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2083)

<223> n equals a,t,g, or c

<400> 234

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<210> 235
 <211> 2143
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (2058)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2080)
 <223> n.equals a,t,g, or c

<220>
 <221> SITE
 <222> (2115)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2132)
 <223> n equals a,t,g, or c

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tcaccaacac	gcttatttttg gcagtggcag catccattgt gtttatcatc tggacaacca 180
tgaagttcag	aatagtgaca tgtcagtcgg actggcgggga gctgtgggta gacgatgcca 240
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154

aat t t t g t t t	a c a a a t g g t g	t a t a t t a a a g	a t t t t t c t a t	t t c a g a t g t a	c t t t a a a g a g	1260
a a t a t t a g c	t t a a c t c t t t	t g a c a t c t g c	t a t t g t g a c a	c a t c c c a t t g	c t g g c a a t g t	1320
g g t g c a c a c t	c c g a a a c t t t	t a a c t a c t g t	t t t g t a a g c c	t c c a a g g g t g	g c a t t g c a g g	1380
g t c c t t a g g c	a a t g t t t t g t	t t g c c t t t a t	g c a g a g a g g t	g c t c c a a g t g	c t g t g a t t g a	1440
g c a c c g t g c t	a g a g g a a c t g	t a a t g c t t c a	g a a g t t g t a g	c t t a t a c a a a	g g a a a c a g g t	1500
c c t g c t g g c t	t a a t t t a a a c	a g t t a t t g c a	t g a a g t a g c g	t g g a g g c c c t	g g a c t g c t g c	1560
t c g t t c t t t a	g g a t g g a c t g	t t c t g g t a t c	t g g t a t t g g t	t t a g a g a c t g	t t a a t a a g g g	1620
a c a t c a c a a g	g t g a t g g g a t	t c a t t t g a a g	c a c t c t a t t t	c t g t t t t a a t	g g t t t t a t c c	1680
a a t t t t g c c t	t c c c a a g a t t	t t t g t t c t a c	a t a a a a a g t t	c a t g c c a c t t	t t t a a t a t a a	1740
a a a a a t t t a a	c a a a a t t a a t	g t a t t t t t c t	c a t t t t t t t c	a a a c t t t t t c	t a a a g a c t c t	1800
t t c t g t c a a a	c t c a t g a a a a	a t t t c t t t c t	a t g g c t t t t a	t t c t a g a t t g	t c t t a t t t t c	1860
t g t t a a a a c c	a a t g a c c a c a	t g a c c a c a a t	c t t c a c t a a c	t c a t a c t g c a	g t g a a a g t g t	1920
t a a c c c t t a g	g t a g t t t c t c	t a c a a c t c t t	t g c t a t g g t g	a t t t t t a a a a	a a g t t t c c t a	1980
g g g a a g t a t c	t c t g a g g g a a	c a g g c a a t c t	g a a g g a a c t g	a c t a t a t t c t	c c a t g g c t a a	2040
g t c c a t t a g g	c c a a a a g n c t	g g g t g g g t a t	t g g t g t c a n	g c t g t c t a t t	g g c a t a t t a a	2100
a a a c g t a g g c	c g g a n g g a a t	a a t t a g g t g	t n a t g c c g g c	g g g		2143

<210> 236

<211> 1133

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (528)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (552)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1133)

<223> n equals a,t,g, or c

<400> 236

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t a a a t g c t t g	a t g a a t a a a c	g c t a a t c c t a	c c t t c c c a g c	c t g a c a c c t c	c c a g t g g a c a	120
c c a c a c t t c a	c t t g a a g c c t	t a g a a a c c t t	t c c c a c c c a t	g c t t c c a g c c	c t g g c t t c a t	180
g t t g c c a t t t	c t c a c c c c c a	g a a c a g g c c g	c c c g c c t g a a	g a a a c t a c a a	g a g c a a g a g a	240
a a c a a c a g a a	a g t g g a g t t t	c g t a a a a g g a	t g g a g a a g g a	g g t g t c a g a t	t t c a t t c a a g	300
a c a g t g g g c a	g a t c a a g a a a	a a g t t t c a g c	c a a t g a a c a a	g a t c g a g a g g	a g c a t a c t a c	360
a t g a t g t g g t	g g a a g t g g c t	g g c c t g a c a t	c c t t c t c c t t	t g g g g a a g a t	g a t g a c t g t c	420
g c t a t g t c a t	g a t c t t c a a a	a a g g a g t t t g	c a c c c t c a g a	t g a a g a g c t a	g a c t c t t a c c	480
g t c g t g g a g a	g g a a t g g g a c	c c c c a g a a g g	c t g a g g a g a a	g c g g a a c n t g	a a g g a g c t g g	540
c c c a g a g g c a	a n g a g g a g g a	g g c a g c c c a g	c a g g g g c c t g	t g g t g g t g a g	c c c t g c c a g c	600
g a c t a c a a g g	a c a a g t a c a g	c c a c c t c a t c	g g c a a g g g a g	c a g c c a a a g a	c g c a g c c c a c	660
a t g c t a c a g g	c c a a t a a g a c	c t a c g g c t g t	k t g c c c g t g g	c c a a t a a g a g	g g a c a c a c g c	720
t c c a t t g a a g	a g g c t a t g a a	t g a g a t c a g a	g c c a a g a a g c	g t c t g c g g c a	g a g t g g g g a a	780
g a g t t g c c g c	c a a c t c c c t a	g g c g c c c c g c	c c a g c t c c c t	t t g a c c c c t g	g g g c a g g g c a	840
g g g g g c a g g g	a g a g a c a a g g	c t g c t g c t a t	t a g a g c c c a t	c c t g g a g c c c	c a c c t c t g a a	900
c c a c c t c c t a	c c a g c t g t c c	c t c a g g c t g g	g g g a a a a c a g	g t g t t t g a t t	t g t c a c c g t t	960
g g a g c t t g g a	t a t g t g c g t g	g c a t g t g t g t	g t g t g t g t g a	g a g t g t g a a t	g c a c a g g t g g	1020
g t a t t t a a t c	t g t a t t a t t c	c c c g t t c t t g	g a a t t t t c t t	c c c a t g g g g c	t g g g g t a c t t	1080
t a c a t t c a a t	a a a t a c t g t t	t a a c c c a a a a	a a a a a a a a a a	a a a a g a a a g a	a g n	1133

<210> 237
 <211> 1025
 <212> DNA
 <213> Homo sapiens

<400> 237
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 cccctgggccc ctggcttaag ccgacactcc tgacctctct gttcaccctg agggctgtct 780
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 aaaaa 1025

<210> 238
 <211> 1400
 <212> DNA
 <213> Homo sapiens

<400> 238
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 ggaaggcata ggttgagaga atgggaagat gragtggagg cgggttggtta aagtgtgtc 180
 agtgagtgat tttgtctact tgaataatgg tccatgtttg ggggcatatt gtgtttcata 240
 agaagtgaag ggtatttgca aagtaagcta caaatgaccc ataaatctgt taacaacagt 300
 ccttaatatg caaagatgaa aaacaagcat tactgtacc caaagggaac tgggtgcttg 360
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 gagttagttc tgaggatggg agtaataaag gagttttttg tttttttgtt tgtttgtttg 540
 ttttggtccc ttagtaatac tcctctgaca tttatttcta ttattcttca aagaaaggaa 600
 accaactgaa atgtttgctt taacaaacat ttaataaagt tctctgggtt tttttttccc 660
 cttttaaaaa aattagcata taccatagca ataaaagaac taatgttaac tattgtatgc 720
 tacaacttaa gtgatttttc taaagaagca caatgtcatt graagtatta ttgaaaagga 780
 tcatagtccac attgaatttg tgaaggccaa agaaattgaa gggagtgata ttttctattt 840
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 atggaaacag gtttcagatt actttgtttt tactgttaga gtctcaagtt tagaaatgct 960
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 tgtaattacc ataaataatg gctagcgaga acatcttttg aaattctcaa attaccttc 1260
 ttactacact gtttgcagaa tgaatgtaga aatgatcctg ttagctttct gaatgttctg 1320
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 aaaaaaaaa aaaaactcga 1400

<210> 239
 <211> 1250
 <212> DNA
 <213> Homo sapiens

<400> 239
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 atsttcgccc tgcgtctgggt cctccactac cgagaggggc ttggctggga tgggagcgca 180
 ctagagttta actggcacc cagtgcstg gtccacggct tgcgtctcat ccagggcac 240
 gcatcatcgt ctacagactg ccgtggacct ggaaatgcag caagctcctg atgaaatcca 300
 tccatgcagg gttaaataca gttgctgcca ttcttgcaat tatctctgtg gtggccgtgt 360
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 ccctgagaga tctgcatac agtacattcc cgccagaagg tgttttcgta aatacgcttg 660
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<210> 240
 <211> 1307
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (651)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1064)
 <223> n equals a,t,g, or c

<400> 240
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 catgartgtc ctttgggtgc tgtttctttt aaatcctctg tgcacagggc tctggccttt 120
 artaaactgt ttttctgtct tacgtcatgc tgactgggtg ctaggggctg attacaaagg 180
 ggaagagttg aacagacatc aggggccgat gaaaccaaag gactaggagt caggagaaca 240
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 gcagcagcag gaggaatacc agggccacgg aggggcagga gtctcacagt ggagggcaga 360
 ctctaacaga tgccagctga acgctcgtcg gccctggatg tcatacagat tggggaccag 420
 aaatctgggc tcagagaacc cgtccaggga gatttgaagc catgggttat cttctagagt 480
 tgatactgat aatatatttt aatttttatt gatgtttaat accttctgaa acaggagggt 540
 aagatcagat gggaagcccy tctgttgaag gatcttggga accttggtgg tttttttttt 600
 ttgggtttttt tttttttgat cgagctgtgg acatccttct taattcgatt ntgaggattt 660

157

gtttaactaa	aaagttccca	aacacagaaa	gggcctcccc	acctgctttg	gggagctgtc	720
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acctgaatgt	tcctactaca	caaataaaca	tatattaaat	wctaaaaaaa	aaaaaaaaaa	1260
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<210> 241

<211> 888

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (830)

<223> n equals a,t,g, or c

<400> 241

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ccccagggac	agtctcaaat	gcaaattccac	agagtgasmc	accacctcgg	gtagaatttg	180
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aacagcaaga	gagacaacgg	atccaactca	tgcaggaggt	agatagacaa	agagctttgc	300
agcagaggat	ggaaatggag	cagcatggta	tggtgggctc	tgagataagt	agtagtagga	360
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taggaccctt	tcagcagttc	ccacaacacc	aacagcaaat	ggggcagggt	ttacagcagc	480
agaatataca	acaaggatca	attaattcac	cctccaccca	aactttcatg	cagactaatg	540
agcgaggcag	gtaggccctc	cttcatttgt	tcctgattca	ccatcaatcc	ctgttggaag	600
cccaaatttt	tcttctgtga	agcaggga	tggaatctt	tctgggacca	gcttccagca	660
gtccccagtg	aggccttctt	ttacacctgc	tttaccagca	gcacctccag	tagctaatag	720
cagtctccca	tgtggccaag	attctactat	aacccatgga	cacagttatc	cgggatcaac	780
ccaatcgctc	attcagttgt	attctgatat	aatcccagag	gaaaaagggn	aaaaaaaaara	840
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<210> 242

<211> 1811

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> SITE

158

<222> (16)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1810)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1811)
 <223> n equals a,t,g, or c

<400> 242
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 ccastgtcat tatcacaaca gtgtctgtcc tgggtcttga cttcaggccc tccctggaat 180
 ttttcttgga agccscatca gtcstyctct ctatatttat ttataatgcc agcaagcctc 240
 aagttccgga atacgcacct aggcaagaaa ggatccgaga tctaagtggc aatctttggg 300
 agcgttccag tggggatgga gaagaactag aaagacttac caaacccaag agtgatgagt 360
 cagatgaaga tacttttctaa ctggtaccca catagtttgc agctctcttg aaccttattt 420
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 aatcctaata ttctttgcat atatctagct actccctaaa tggttccatc caaggcttag 540
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 attaatatct cagtacttga taaatcagaa agttatatgt gcagattatt ttccttggcc 660
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 gatcaatttg ccaaatattc acaatcatgt agttctagtt tacatgccaa agtcttccct 780
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 aaaaaaaaaa n 1811

<210> 243
 <211> 2271
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (553)
 <223> n equals a,t,g, or c

<220>

<221> SITE
 <222> (2267)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2269)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2271)
 <223> n equals a,t,g, or c

<400> 243

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atccaagccc	ttgtgggggt	ggcgcgcccg	ctggtcttgg	cgctcctgct	tgtgtccgcc	180
gctctatcca	gtgtgtatc	acggactgat	tcaccgagcc	caaccgtact	caactcacat	240
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caaatacgca	ccaccctccc	tcccacgacg	agtaccaaga	aaagtggagg	agcatctgtg	360
gtccctcatc	cctcgccctac	tcctctgtct	caagaggaag	ctgataacaa	tgaagatcct	420
agtatagagg	aggaggatct	tctcatgctg	aacagttctc	catccacagc	caaagacact	480
ctagacaatg	gcgattatgg	agaaccagac	tatgactgga	ccacggggccc	cagggacgac	540
gacgagtctg	atngacacct	tggaagaaaa	caggggttac	atggaaattg	aacagtcagt	600
gaaatctttt	aagatgccat	cctcaaatat	agaagaggaa	gacagccatt	tcttttttca	660
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<210> 244
 <211> 2500
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2459)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2473)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2475)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2478)

<223> n equals a,t,g, or c

<400> 244

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aaatattatt	cctacagtaa	agaaaatagt	tctgcttgca	ggatgggcat	tgttcttatt	360
ccttgcatat	aaagtttcca	aaacagaccg	agaataccaa	gaatacaatc	cttatgaagt	420
attaaatttg	gatcctggag	ccacagtagc	agaaattaaa	aaacaatatc	gtttgctgtc	480
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161

tcattgtgtgt	acgctgaaag	atacagagga	ggtagagctg	aagtttcctg	caccaggcaa	2160
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<210> 245

<211> 1338

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (133)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (867)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1338)

<223> n equals a,t,g, or c

<400> 245

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gccagcgtgg	cgngcctggc	ggctcccggg	tggtgagaga	gcggtccggg	aacgatgaag	180
gcctcgagct	gctgctgctg	tctcagccac	ctcttggtct	ccgtcctcct	cctgctgttg	240
ctgctgaac	taagcgggyc	cctggmagtc	ctgctgcagg	cagccgaggc	cgcgccagggt	300
yttgggcttc	ctgaccctag	accaggacat	taccgcccgt	gccaccgggc	cctwaccctt	360
gcccagcagc	cgggcccgtg	tctggctgaa	gctgcggggg	ccgcccgggt	ccgaggggagg	420
caatggcagc	aacctgtggg	ccgggcttga	gacggacgat	cacggaggga	aggccgggga	480
argctcggtg	ggtggcgggc	ttgctgtgag	ccccaaccct	ggcgacaagc	ccatgaccca	540
gcgggcccctg	accgtgttga	tggtggtgag	cggcgcggtg	ctggtgtact	tcgtggtcag	600
gacggtcagg	atgagaagaa	gaaaccgaaa	gactaggaga	tatggagttt	tggaactaa	660
catagaaaat	atggaattga	cacctttaga	acaggatgat	gaggatgatg	acaacacggt	720
gtttgatgcc	aatcatcctc	gaagataaga	atgtgccttt	tgatgaaaga	actttatctt	780
tctacaatga	agagtggaa	ttctatgttt	aaggaataag	aagccactat	atcaatgttg	840
gggggggtatt	taagttacat	atattttnac	aacctttaat	ttgctgttgc	aataaatacc	900
gtatcctttt	attatatctt	tatatgtata	gaagtactct	gttaatgggc	tcagagatgt	960
tggggataaaa	gtatactgta	ataatttatc	tgtttgaaaa	ttactataaa	acggtgtttt	1020
ctgrtcgggt	tttgtttcct	gcttaccata	tgattgtaaa	ttgttttatg	tattaatcag	1080
ttaatgctaa	ttatttttgc	tgatgtcata	tgtaaaagag	ctataaattc	caacaaccaa	1140
ctggtgtgta	aaaataattt	aaaatytcct	ttactgaaag	gtatttccca	tttttgtggg	1200
gaaaagaagc	caaatttatt	actttgtgtt	gggggtttta	aaatattaag	aaatgtctaa	1260
gttattgttt	gcaaaacaat	aaatatgatt	ttaaattctc	ttaaaaaaa	aaaaaaaaac	1320
cccggggggg	ggccccgn					1338

<210> 246

<211> 654

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (651)

<223> n equals a,t,g, or c

<400> 246

gaattcggca	cgaggcagct	tgtgctttaa	aggaggtgtt	caaagcatgt	ctgagcagag	60
acttttgggc	tctgttttaa	ttaatacttt	aaaataattc	atatttataa	tatcaratgt	120
ttccataaag	aggaggatgt	ttaaatgcct	ccagactaca	ttccttttta	ttsccttgatt	180
ttacctggga	gtccaaagtt	caattcccat	aaagcaagcg	ttttatttgt	cactttcaat	240
atacatccga	ttgccatgct	taagatgcaa	tatgggctgc	ggaaataggt	taaccacacag	300
gctcccaggg	cccagtgtag	aagggtgagag	attcgtgtaa	aatgattcaa	ataaaaggaa	360
gaccctggcc	gggtgccgta	rctcacgcct	gtaatcccag	cactttggga	ggccgaagcg	420
agtggatgac	gaggtttagga	gttgagagacc	agcctggcca	acatcgtgaa	accccgctctc	480
tactaaaaat	acaaaaatta	gccgggcatg	gtggcaggca	cctgtaatcc	tagctagtgtg	540
ggaggctgag	gcaggagaat	cgtttgaatc	tgggagttgg	aggttgtcag	tgagctgaga	600
tcgcgccaca	gcactccagc	ctgggtgaca	gggtgagact	ctgtctcaaa	naga	654

<210> 247

<211> 1146

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (35)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (36)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (37)

<223> n equals a,t,g, or c

<400> 247

aaaaaaaaacc	caggggaacn	ttgggggccg	ctttnnnttc	cccctccagg	ccattgggga	60
attcttcaag	ttaatcctgc	tttgctcttg	gccaacaggg	cttgtagggg	ggagagaccc	120
aggatcatca	aggggttcga	gtgcaagcct	cactcccagc	cctggcaggc	agccctgttc	180
gagaagacgc	ggctactctg	tggggcgacg	ctcatcgccc	ccagatggct	cctgacagca	240
gccactgcc	tcaagccccg	ctacatagtt	cacctggggc	agcacaacct	ccagaaggag	300
gagggctgtg	agcagacccg	gacagccact	gagtccttcc	cccaccccgg	cttcaacaac	360
agcctcccca	acaaagacca	ccgcaatgac	atcatgctgg	tgaagatggc	atcgccagtc	420
tccatcacct	gggctgtgcg	accctcacc	ctctcctcac	gctgtgtcac	tgctggcacc	480
agctgyctca	tttcggctg	gggcagmacg	tccagcccc	agttaagcct	gcctcacacc	540
ttgsgatgcg	ccaacatcac	catcattgag	caccagaagt	gtgagaacgc	ctaccccggc	600
aacatcacag	acaccatggt	gtgtgccagc	gtgcaggaag	ggggcaagga	ctcctgccag	660

ggtgactccg	ggggccctct	ggtctgtaac	cagtctcttc	aaggcattat	ctcctggggc	720
caggatccgt	gtgcgatcac	ccgaaagcct	ggtgtctaca	cgaaagtctg	caaatatgtg	780
gactggatcc	aggagacgat	gaagaacaat	tagactggac	ccaccacca	cagcccatca	840
ccctccattt	ccacttggtg	tttggttcct	gttactctg	ttaataagaa	accctaagcc	900
aagaccctct	acgaacattc	tttgggcctc	ctggactaca	ggagatgctg	tcacttaata	960
atcaacctgg	ggttcgaaat	cagtgagacc	tggattcaaa	ttctgccttg	aaatattgtg	1020
actctgggaa	tgacaacacc	tggtttgttc	tctgttgat	ccccagcccc	aaagacagct	1080
cctggccata	tatcaagggt	tcaataaata	tttgctaaat	gaaaaaaaaa	aaaaaaaaaa	1140
actcga						1146

<210> 248

<211> 1443

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (776)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (907)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1288)

<223> n equals a,t,g, or c

<400> 248

ataaactgaa	ataggatcatg	caaatataaa	atattatattt	taaattatatt	gtcataagaa	60
acgatgggtg	ccatattttg	ctttaataat	ggaaaaaatg	tggttagcat	tctktggaag	120
gtggatcatca	gatagtagac	atatttctagg	atattatattt	acctgcatat	gtggaaatgt	180
gtactacttt	agattttatwt	aatggcagct	aactcagagg	catcaaaatg	tgctaattggt	240
gtaatatggc	ctttgtcttg	ctgtyctgtt	ttgtargcct	tcaatcaagc	argggcaggg	300
ccgtacagtg	aacttgtcct	ttgscagacg	ccagcgtctg	cccctgaccc	cgtctccact	360
ctctgtgtcc	tggaggagga	gccccttgat	gcytaccctg	attcaccttc	tgcgtgcctt	420
gtactgaact	gggaagagcc	gtgcaataac	ggatctgaaa	tccttgctta	caccattgat	480
ctaggagaca	ctagcattac	cgtgggcaac	accaccatgc	atgttatgaa	agatctcctt	540
ccagaaacca	cctaccggtg	agtgcagggt	agtagaaatc	tgcatcagca	catcagcact	600
tggggatcta	agtaaacctc	tcggggaaaa	tgaccaagtg	gatgtcatct	cccagctgtt	660
tctaagagcc	cagatgtcca	gagtattgtc	tcaccttgat	ccctcaggcc	agaagacctg	720
tgaaaaagcc	acactggttc	agggactcac	tggacggttt	tgtgtccact	ytacntgca	780
ccgtctctac	cccagagtgg	actcaratcc	tcaagtcac	ctctgaacat	tgrrgtcaga	840
aattataaaa	gggctttggc	aatatgttag	cccaagaatt	tggcttcttc	cagaaattgt	900
gccgacntta	acagtggctt	aaatgatggt	aaaactttta	agatttctaa	aaggrrtgga	960
ttggagatac	gttgactttt	attaaacmac	ctatagttgt	ttaatgaytt	ctaaaaaat	1020
atctggagct	caggggttca	actgaggga	cacatgttga	gratcattgt	ttactaatta	1080
aatgccaggt	aaccggttga	aattatcaaa	aacatcttcc	acgtaccaga	aagcacctca	1140
gaggatagtt	ctgttatgga	gaagatgaaa	tggtttagta	gtgtagggaac	tatggaaagg	1200
tgagcttaga	tttggatagt	aaaacctcaa	gacctatatt	aaaaagtatt	ttatgaatgc	1260
agcataaata	atttaattca	gtgttaanat	gccaaggcta	gtatattgag	ctgaatgtga	1320
aaagaaactc	acattgggag	aatgccacct	tttccctata	agatagcttt	gaagatacca	1380
ttttagacag	atggaaattg	aatagcttta	gaaaaggcaa	atgtttgatc	ttggggaaaa	1440
aaa						1443

164

<210> 249
 <211> 31
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals stop translation

<400> 249
 Met Leu Ser Thr Gly Ile Glu Val Ala Arg Pro Pro Ala Thr Leu Leu
 1 5 10 15
 Gly Leu Met Phe Val Leu Thr Gly Met Pro Arg Gly Leu Arg Xaa
 20 25 30

<210> 250
 <211> 116
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (36)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (78)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (116)
 <223> Xaa equals stop translation

<400> 250
 Met Asn Val Val Ile Val Ile Ile Leu Phe Ser Phe Asp Ser Val Gly
 1 5 10 15
 Thr Met Phe Ser Cys Asn Arg Ile Pro Lys Ile Thr Val Leu Asn Lys
 20 25 30
 Leu Lys Phe Xaa Cys Glu Val Leu Leu Arg Ile Gln Thr Ile Gln Gly
 35 40 45
 Phe Tyr Arg Cys Thr Arg Ile Ser Arg Tyr Lys Gly Ile Phe Pro Asp
 50 55 60
 Phe Cys Gln Ser Gln Cys Met Gly Cys Asn Pro Glu Ser Xaa Met Ala
 65 70 75 80
 Val Pro Ala Leu Val Thr Pro Ile Leu Ala His Arg Lys Lys Glu Lys
 85 90 95

165

Gly Met Cys Leu Phe Thr Leu Ile Ile Ala Pro Thr Arg Cys Thr His
 100 105 110

Tyr Phe Cys Xaa
 115

<210> 251
 <211> 103
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (103)
 <223> Xaa equals stop translation

<400> 251
 Met Ser Ser Ala Lys Ile Val Arg Gln Arg Gly Ala Val Pro Thr Tyr
 1 5 10 15
 Tyr Thr Thr Glu Ala Gly Glu Ile Ile Phe Leu Val Leu Asn Trp Ser
 20 25 30
 Leu Ser Ile Leu His Ile Val Asp Val Leu Cys Ser Lys Pro Glu Lys
 35 40 45
 Ser Val Thr Glu Asp Ala Ala Ser Gly Leu Ser Gln Arg Met Thr Ala
 50 55 60
 Leu Val Trp Arg Lys Gly Pro Asp Gly Gly Ser Arg Lys Pro Ile Leu
 65 70 75 80
 Leu Leu Phe Phe Phe Leu Pro Leu Ile Leu Cys Phe His Ser Phe Ile
 85 90 95
 His Ser Ser Asn Ile Cys Xaa
 100

<210> 252
 <211> 42
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (13)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (22)

166

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 252

Met Ile Leu Phe Pro Gln Xaa Ala Leu Arg Leu Gly Xaa Trp Pro Arg
1 5 10 15

Thr Trp Ser Ile Leu Xaa Lys Tyr Ser Val Asn Phe Phe Ser Ala Tyr
20 25 30

Ser Pro Met Gly Ala Val Gly Thr Glu Phe
35 40

<210> 253

<211> 37

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (32)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals stop translation

<400> 253

Met Ile Ile Leu Leu Leu Phe Met Leu Leu Asn Asn Val Val Leu Val
1 5 10 15

Gln Glu Asp Asn Cys Gln Arg Lys Asn Thr Val Gln Glu Arg Arg Xaa
20 25 30

Trp Ser Gln Trp Xaa
35

<210> 254

<211> 128

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (128)

<223> Xaa equals stop translation

167

<400> 254

Met Ala Ala Xaa Pro Pro Gly Cys Thr Pro Pro Xaa Leu Leu Asp Ile
 1 5 10 15

Ser Trp Leu Thr Glu Ser Leu Gly Ala Gly Gln Pro Val Pro Val Glu
 20 25 30

Cys Arg His Arg Leu Glu Val Ala Gly Pro Arg Lys Gly Pro Leu Ser
 35 40 45

Pro Ala Trp Met Pro Ala Tyr Ala Cys Gln Arg Pro Thr Pro Leu Thr
 50 55 60

His His Asn Thr Gly Leu Ser Glu Leu Leu Glu His Gly Val Cys Glu
 65 70 75 80

Glu Val Glu Arg Val Arg Arg Ser Glu Arg Tyr Gln Thr Met Lys Val
 85 90 95

Arg Arg Ala Gly Leu Gly Pro Thr Pro Gly Met Ser Cys Pro Gly Asn
 100 105 110

Asp Asn Thr Val His Thr Met His Gly Glu Ala Asn Arg Gly Ser Xaa
 115 120 125

<210> 255

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (67)

<223> Xaa equals stop translation

<400> 255

Met Ser Ile Leu Cys Cys Pro Xaa Leu Cys Leu Phe Phe Ser Phe Cys
 1 5 10 15

Ile Ser Ser Gly Ser Cys Pro Phe Ser His Val Ser Gln Leu Ser Phe
 20 25 30

Ile Ala Thr Phe Ser Gln Ser Ser Pro Val Leu Leu Val Pro Ala Tyr
 35 40 45

Asn Thr Tyr Leu Ser Phe Leu Ala Phe Leu Asp Cys Ala Ser Leu Thr
 50 55 60

168

Ser Thr Xaa
65

<210> 256
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (69)
<223> Xaa equals stop translation

<400> 256
Met Ser Thr Phe Gln Leu Leu Leu Leu Ile Leu Ala Gln Ser Thr Tyr
1 5 10 15

Lys Ile Lys Ser Lys Pro Leu His Met Thr Asn His Thr Leu Leu Asn
20 25 30

Ser Pro Gly Leu Asn Pro Ser Ser Pro Thr Leu Asn Phe Lys Thr Gln
35 40 45

Gln His Glu Ser Val Ser Tyr Ala Cys Cys His Met Arg Ser Leu His
50 55 60

His Ala Phe Ala Xaa
65

<210> 257
<211> 44
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (36)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (44)
<223> Xaa equals stop translation

<400> 257
Met Val Ser Val Val Leu Ile Phe Ser Phe Leu Ser Leu Thr Ile Ser
1 5 10 15

Thr Thr Ala Ser Ala Tyr Asn Gly Asn Asp Thr Gln Gly Trp Asn Asp
20 25 30

169

Lys Phe His Xaa Xaa Ser Val Lys Thr Gln Thr Xaa
35 40

<210> 258
<211> 51
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (51)
<223> Xaa equals stop translation

<400> 258
Met Ile Ser Asp Ala Gly Ala Gly Phe Gly Val Phe Leu Leu Val Pro
1 5 10 15

Arg Ala Gly His Cys Trp Gly Ala Gly Lys Pro Leu Pro Ser Cys Pro
20 25 30

Ser Val Ala Ser Ile Pro Ser Trp Val Leu Pro Ser Phe Leu Glu Arg
35 40 45

Gly Arg Xaa
50

<210> 259
<211> 43
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals stop translation

<400> 259
Met Val Gln Thr Ile Gln Asp Phe Leu Ser Leu Phe Ser Thr Pro Ile
1 5 10 15

Phe Leu Leu Leu Leu Met Phe Glu Thr Leu Ser Leu Ala Pro Ala Trp
20 25 30

Leu Lys Pro Leu Arg Val Thr Ser His Ser Xaa
35 40

<210> 260
<211> 61
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (61)
<223> Xaa equals stop translation

170

<400> 260

Met Ile Leu Met Pro Gly Leu Gly Thr Ser Arg Gln Arg Ser Val Pro
 1 5 10 15

Phe Val Pro Thr Leu Asn Ala Ser Thr Pro Gly Ala Met Thr Gly Pro
 20 25 30

Thr Ala Thr Leu Thr Ser Cys Gln Trp Thr Thr Ala Cys Arg Val Ser
 35 40 45

Trp Ala Asn Gly Trp Thr Ser Leu Arg Thr Phe Arg Xaa
 50 55 60

<210> 261

<211> 36

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (36)

<223> Xaa equals stop translation

<400> 261

Met Ser His His Ala Gln Pro Arg Phe Leu Leu Ile Thr Met Leu Leu
 1 5 10 15

Gln Glu Ala Lys Pro Val Ser Asn Ile Pro His Leu Leu Glu Ser Trp
 20 25 30

Tyr Phe Gly Xaa
 35

<210> 262

<211> 38

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (38)

<223> Xaa equals stop translation

<400> 262

Met Asn Ser Leu Phe Trp Met Ile Leu Leu Pro Val Ser Gln Asp Gln
 1 5 10 15

Val Val Glu Gly Leu Gln Gly Gly Phe Ser Gln Ile His Met Arg Ile
 20 25 30

Leu Arg Lys His Leu Xaa
 35

<210> 263

171

<211> 211
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (5)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (211)
 <223> Xaa equals stop translation

<400> 263

Met Ser Arg Ser Xaa Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala
 1 5 10 15

Ala Ser Ile Tyr Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala
 20 25 30

Leu His Gln Gly Asp Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile
 35 40 45

Leu Leu Lys Leu Asp Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg
 50 55 60

Met Gln Asp Leu Asp Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala
 65 70 75 80

Trp Val Ser Leu Ala Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr
 85 90 95

Ile Phe Gln Glu Met Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu
 100 105 110

Asn Gly Gln Ala Ala Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala
 115 120 125

Glu Gly Leu Leu Gln Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu
 130 135 140

Thr Leu Val Asn Leu Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro
 145 150 155 160

Glu Val Thr Asn Arg Tyr Leu Ser Gln Leu Lys Asp Ala His Arg Ser
 165 170 175

His Pro Phe Ile Lys Glu Tyr Gln Ala Lys Glu Asn Asp Phe Asp Arg
 180 185 190

Leu Val Leu Gln Tyr Ala Pro Ser Ala Glu Ala Gly Pro Glu Leu Ser
 195 200 205

Gly Pro Xaa
 210

172

<210> 264
 <211> 548
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (548)
 <223> Xaa equals stop translation

<400> 264

Met	Glu	Asp	Ser	Glu	Ala	Leu	Gly	Phe	Glu	His	Met	Gly	Leu	Asp	Pro	1	5	10	15
Arg	Leu	Leu	Gln	Ala	Val	Thr	Asp	Leu	Gly	Trp	Ser	Arg	Pro	Thr	Leu	20	25	30	
Ile	Gln	Glu	Lys	Ala	Ile	Pro	Leu	Ala	Leu	Glu	Gly	Lys	Asp	Leu	Leu	35	40	45	
Ala	Arg	Ala	Arg	Thr	Gly	Ser	Gly	Lys	Thr	Ala	Ala	Tyr	Ala	Ile	Pro	50	55	60	
Met	Leu	Gln	Leu	Leu	Leu	His	Arg	Lys	Ala	Thr	Gly	Pro	Val	Val	Glu	65	70	75	80
Gln	Ala	Val	Arg	Gly	Leu	Val	Leu	Val	Pro	Thr	Lys	Glu	Leu	Ala	Arg	85	90	95	
Gln	Ala	Gln	Ser	Met	Ile	Gln	Gln	Leu	Ala	Thr	Tyr	Cys	Ala	Arg	Asp	100	105	110	
Val	Arg	Val	Ala	Asn	Val	Ser	Ala	Ala	Glu	Asp	Ser	Val	Ser	Gln	Arg	115	120	125	
Ala	Val	Leu	Met	Glu	Lys	Pro	Asp	Val	Val	Val	Gly	Thr	Pro	Ser	Arg	130	135	140	
Ile	Leu	Ser	His	Leu	Gln	Gln	Asp	Ser	Leu	Lys	Leu	Arg	Asp	Ser	Leu	145	150	155	160
Glu	Leu	Leu	Val	Val	Asp	Glu	Ala	Asp	Leu	Leu	Phe	Ser	Phe	Gly	Phe	165	170	175	
Glu	Glu	Glu	Leu	Lys	Ser	Leu	Leu	Cys	His	Leu	Pro	Arg	Ile	Tyr	Gln	180	185	190	
Ala	Phe	Leu	Met	Ser	Ala	Thr	Phe	Asn	Glu	Asp	Val	Gln	Ala	Leu	Lys	195	200	205	
Glu	Leu	Ile	Leu	His	Asn	Pro	Val	Thr	Leu	Lys	Leu	Gln	Glu	Ser	Gln	210	215	220	
Leu	Pro	Gly	Pro	Asp	Gln	Leu	Gln	Gln	Phe	Gln	Val	Val	Cys	Glu	Thr	225	230	235	240
Glu	Glu	Asp	Lys	Phe	Leu	Leu	Leu	Tyr	Ala	Leu	Leu	Lys	Leu	Ser	Leu	245	250	255	

Ile Arg Gly Lys Ser Leu Leu Phe Val Asn Thr Leu Glu Arg Ser Tyr
 260 265 270
 Arg Leu Arg Leu Phe Leu Glu Gln Phe Ser Ile Pro Thr Cys Val Leu
 275 280 285
 Asn Gly Glu Leu Pro Leu Arg Ser Arg Cys His Ile Ile Ser Gln Phe
 290 295 300
 Asn Gln Gly Phe Tyr Asp Cys Val Ile Ala Thr Asp Ala Glu Val Leu
 305 310 315 320
 Gly Ala Pro Val Lys Gly Lys Arg Arg Gly Arg Gly Pro Lys Gly Asp
 325 330 335
 Lys Ala Ser Asp Pro Glu Ala Gly Val Ala Arg Gly Ile Asp Phe His
 340 345 350
 His Val Ser Ala Val Leu Asn Phe Asp Leu Pro Pro Thr Pro Glu Ala
 355 360 365
 Tyr Ile His Arg Ala Gly Arg Thr Ala Arg Ala Asn Asn Pro Gly Ile
 370 375 380
 Val Leu Thr Phe Val Leu Pro Thr Glu Gln Phe His Leu Gly Lys Ile
 385 390 395 400
 Glu Glu Leu Leu Ser Gly Glu Asn Arg Gly Pro Ile Leu Leu Pro Tyr
 405 410 415
 Gln Phe Arg Met Glu Glu Ile Glu Gly Phe Arg Tyr Arg Cys Arg Asp
 420 425 430
 Ala Met Arg Ser Val Thr Lys Gln Ala Ile Arg Glu Ala Arg Leu Lys
 435 440 445
 Glu Ile Lys Glu Glu Leu Leu His Ser Glu Lys Leu Lys Thr Tyr Phe
 450 455 460
 Glu Asp Asn Pro Arg Asp Leu Gln Leu Leu Arg His Asp Leu Pro Leu
 465 470 475 480
 His Pro Ala Val Val Lys Pro His Leu Gly His Val Pro Asp Tyr Leu
 485 490 495
 Val Pro Pro Ala Leu Arg Gly Leu Val Arg Pro His Lys Lys Arg Lys
 500 505 510
 Lys Leu Ser Ser Ser Cys Arg Lys Ala Lys Arg Ala Lys Ser Gln Asn
 515 520 525
 Pro Leu Arg Ser Phe Lys His Lys Gly Lys Lys Phe Arg Pro Thr Ala
 530 535 540
 Lys Pro Ser Xaa
 545

174

<210> 265

<211> 299

<212> PRT

<213> Homo sapiens

<400> 265

Met Thr Thr Val Pro Pro Ser Pro Arg Pro Met Ser Arg Pro Ser Glu
 1 5 10 15

Arg Asn Met Arg Arg Pro Arg Gly Pro Ser Pro Leu Pro Ala Ser Pro
 20 25 30

Arg Asn Ser Thr Pro Asp Glu Pro Asp Val His Phe Ser Lys Lys Phe
 35 40 45

Leu Asn Val Phe Met Ser Gly Arg Ser Arg Ser Ser Ser Ala Glu Ser
 50 55 60

Phe Gly Leu Phe Ser Cys Ile Ile Asn Gly Glu Glu Gln Glu Gln Thr
 65 70 75 80

His Arg Ala Ile Phe Arg Phe Val Pro Arg His Glu Asp Glu Leu Glu
 85 90 95

Leu Glu Val Asp Asp Pro Leu Leu Val Glu Leu Gln Ala Glu Asp Tyr
 100 105 110

Trp Tyr Glu Ala Tyr Asn Met Arg Thr Gly Ala Arg Gly Val Phe Pro
 115 120 125

Ala Tyr Tyr Ala Ile Glu Val Thr Lys Glu Pro Glu His Met Ala Ala
 130 135 140

Leu Ala Lys Asn Ser Asp Trp Val Asp Gln Phe Arg Val Lys Phe Leu
 145 150 155 160

Gly Ser Val Gln Val Pro Tyr His Lys Gly Asn Asp Val Leu Cys Ala
 165 170 175

Ala Met Gln Lys Ile Ala Thr Thr Arg Arg Leu Thr Val His Phe Asn
 180 185 190

Pro Pro Ser Ser Cys Val Leu Glu Ile Ser Val Arg Gly Val Lys Ile
 195 200 205

Gly Val Lys Ala Asp Asp Ser Gln Glu Ala Lys Gly Asn Lys Cys Ser
 210 215 220

His Phe Phe Gln Leu Lys Asn Ile Ser Phe Cys Gly Tyr His Pro Lys
 225 230 235 240

Asn Asn Lys Tyr Phe Gly Phe Ile Thr Lys His Pro Ala Asp His Arg
 245 250 255

Phe Ala Cys His Val Phe Val Ser Glu Asp Ser Thr Lys Ala Leu Ala
 260 265 270

175

Glu Ser Val Gly Arg Ala Phe Gln Gln Phe Tyr Lys Gln Phe Val Glu
 275 280 285

Tyr Thr Cys Pro Thr Glu Asp Ile Tyr Leu Glu
 290 295

<210> 266

<211> 40

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (40)

<223> Xaa equals stop translation

<400> 266

Leu Leu Tyr Leu Leu Lys Val Xaa Val Ile Phe Val Phe Ser Ser Ser
 1 5 10 15

Lys Gly Val Thr Leu Val Ser Met Asn Leu Thr Ser Phe Phe Val Ser
 20 25 30

Ser Val Leu Ala Cys Phe Ser Xaa
 35 40

<210> 267

<211> 594

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (99)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 267

Met Pro Ala Ser Ser Leu Glu Ser Arg Ser Phe Leu Leu Ala Lys Lys
 1 5 10 15

Ser Gly Glu Asn Val Ala Lys Phe Ile Ile Asn Ser Tyr Pro Lys Tyr
 20 25 30

Phe Gln Lys Asp Ile Ala Glu Pro His Ile Pro Cys Leu Met Pro Glu
 35 40 45

Tyr Phe Glu Pro Gln Ile Lys Asp Ile Ser Glu Ala Ala Leu Lys Glu
 50 55 60

Arg Ile Glu Leu Arg Lys Val Lys Ala Ser Val Asp Met Phe Asp Gln
 65 70 75 80

176

Leu Leu Gln Ala Gly Thr Thr Val Ser Leu Glu Thr Thr Asn Ser Leu
 85 90 95
 Leu Asp Xaa Leu Cys Tyr Tyr Gly Asp Gln Glu Pro Ser Thr Asp Tyr
 100 105 110
 His Phe Gln Gln Thr Gly Gln Ser Glu Ala Leu Glu Glu Glu Asn Asp
 115 120 125
 Glu Thr Ser Arg Arg Lys Ala Gly His Gln Phe Gly Val Thr Trp Arg
 130 135 140
 Ala Lys Asn Asn Ala Glu Arg Ile Phe Ser Leu Met Pro Glu Lys Asn
 145 150 155 160
 Glu His Ser Tyr Cys Thr Met Ile Arg Gly Met Val Lys His Arg Ala
 165 170 175
 Tyr Glu Gln Ala Leu Asn Leu Tyr Thr Glu Leu Leu Asn Asn Arg Leu
 180 185 190
 His Ala Asp Val Tyr Thr Phe Asn Ala Leu Ile Glu Ala Thr Val Cys
 195 200 205
 Ala Ile Asn Glu Lys Phe Glu Glu Lys Trp Ser Lys Ile Leu Glu Leu
 210 215 220
 Leu Arg His Met Val Ala Gln Lys Val Lys Pro Asn Leu Gln Thr Phe
 225 230 235 240
 Asn Thr Ile Leu Lys Cys Leu Arg Arg Phe His Val Phe Ala Arg Ser
 245 250 255
 Pro Ala Leu Gln Val Leu Arg Glu Met Lys Ala Ile Gly Ile Glu Pro
 260 265 270
 Ser Leu Ala Thr Tyr His His Ile Ile Arg Leu Phe Asp Gln Pro Gly
 275 280 285
 Asp Pro Leu Lys Arg Ser Ser Phe Ile Ile Tyr Asp Ile Met Asn Glu
 290 295 300
 Leu Met Gly Lys Arg Phe Ser Pro Lys Asp Pro Asp Asp Asp Lys Phe
 305 310 315 320
 Phe Gln Ser Ala Met Ser Ile Cys Ser Ser Leu Arg Asp Leu Glu Leu
 325 330 335
 Ala Tyr Gln Val His Gly Leu Leu Lys Thr Gly Asp Asn Trp Lys Phe
 340 345 350
 Ile Gly Pro Asp Gln His Arg Asn Phe Tyr Tyr Ser Lys Phe Phe Asp
 355 360 365
 Leu Ile Cys Leu Met Glu Gln Ile Asp Val Thr Leu Lys Trp Tyr Glu
 370 375 380

177

Asp Leu Ile Pro Ser Ala Tyr Phe Pro His Ser Gln Thr Met Ile His
 385 390 395 400
 Leu Leu Gln Ala Leu Asp Val Ala Asn Arg Leu Glu Val Ile Pro Lys
 405 410 415
 Ile Trp Lys Asp Ser Lys Glu Tyr Gly His Thr Phe Arg Ser Asp Leu
 420 425 430
 Arg Glu Glu Ile Leu Met Leu Met Ala Arg Asp Lys His Pro Pro Glu
 435 440 445
 Leu Gln Val Ala Phe Ala Asp Cys Ala Ala Asp Ile Lys Ser Ala Tyr
 450 455 460
 Glu Ser Gln Pro Ile Arg Gln Thr Ala Gln Asp Trp Pro Ala Thr Ser
 465 470 475 480
 Leu Asn Cys Ile Ala Ile Leu Phe Leu Arg Ala Gly Arg Thr Gln Glu
 485 490 495
 Ala Trp Lys Met Leu Gly Leu Phe Arg Lys His Asn Lys Ile Pro Arg
 500 505 510
 Ser Glu Leu Leu Asn Glu Leu Met Asp Ser Ala Lys Val Ser Asn Ser
 515 520 525
 Pro Ser Gln Ala Ile Glu Val Val Glu Leu Ala Ser Ala Phe Ser Leu
 530 535 540
 Pro Ile Cys Glu Gly Leu Thr Gln Arg Val Met Ser Asp Phe Ala Ile
 545 550 555 560
 Asn Gln Glu Gln Lys Glu Ala Leu Ser Asn Leu Thr Ala Leu Thr Ser
 565 570 575
 Asp Ser Asp Thr Asp Ser Ser Ser Asp Ser Asp Ser Asp Thr Ser Glu
 580 585 590

Gly Lys

<210> 268

<211> 131

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (131)

<223> Xaa equals stop translation

<400> 268

Met Lys Leu Asn Leu Cys Ile Pro Asn Trp Ala Arg Cys Pro Leu Leu
 1 5 10 15

Leu Leu Phe Pro Gln Leu Leu Pro Phe Gln Gly Glu Asp Asp Asp Pro

178

20 25 30
 Leu Lys Ala Lys Ala Ala Asn Leu Val Glu Ala Val Pro Trp Gly Ile
 35 40 45
 Lys Ala Pro Ser Phe Gln Val Thr Cys Leu Val Arg Val Gln Leu Gln
 50 55 60
 Ser Cys Thr Pro Ser Arg Pro Ser Thr Leu Leu Ala Thr Ser Gln Ser
 65 70 75 80
 Pro Gly Arg Ile Ser Cys Tyr Ser Pro Leu Ser His Leu Pro Pro Val
 85 90 95
 Thr Thr Ser Ile Gln Pro Ser Pro Val Met Val Pro Phe Gln Tyr Gln
 100 105 110
 Ala Phe Leu Leu Gln Val Lys Glu Pro Ala Ala Gln Thr Leu Leu Gly
 115 120 125
 Gln Gln Xaa
 130

<210> 269

<211> 21

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (21)

<223> Xaa equals stop translation

<400> 269

Met Arg Tyr His Ala Gln Leu Ile Phe Cys Ile Phe Cys Xaa Phe Val
 1 5 10 15

Phe Val Xaa Lys Xaa
 20

<210> 270

<211> 159

<212> PRT

<213> Homo sapiens

<220>

179

<221> SITE
 <222> (109)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (118)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (122)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (127)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 270
 Met Thr Gly Thr Tyr Ser Gly Gln Phe Val Met Glu Gly Phe Leu Asn
 1 5 10 15
 Leu Lys Trp Ser Arg Phe Ala Arg Val Val Leu Thr Arg Ser Ile Ala
 20 25 30
 Ile Ile Pro Thr Leu Leu Val Ala Val Phe Gln Asp Val Glu His Leu
 35 40 45
 Thr Gly Met Asn Asp Phe Leu Asn Val Leu Gln Ser Leu Gln Leu Pro
 50 55 60
 Phe Ala Leu Ile Pro Ile Leu Thr Phe Thr Ser Leu Arg Pro Val Met
 65 70 75 80
 Ser Asp Phe Ala Asn Gly Leu Gly Trp Arg Ile Ala Gly Gly Ile Trp
 85 90 95
 Ser Tyr His Leu Phe His His Met Tyr Phe Val Val Xaa Tyr Val Arg
 100 105 110
 Asp Leu Arg His Val Xaa Leu Tyr Val Xaa Ala Ala Val Val Xaa Arg
 115 120 125
 Gly Leu Ser Gly Leu Cys Val Leu Leu Gly Leu Ala Met Phe Asp Cys
 130 135 140
 Thr Gly His Val Leu Pro Gly Leu Trp Ala Tyr Gly Lys His Leu
 145 150 155

 <210> 271
 <211> 219
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE

180

<222> (219)

<223> Xaa equals stop translation

<400> 271

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Met His Phe Leu Phe Arg Phe Ile Val Phe Phe Tyr Leu Trp Gly Leu
 1           5           10           15

Phe Thr Ala Gln Arg Gln Lys Lys Glu Glu Ser Thr Glu Glu Val Lys
      20           25           30

Ile Glu Val Leu His Arg Pro Glu Asn Cys Ser Lys Thr Ser Lys Lys
      35           40           45

Gly Asp Leu Leu Asn Ala His Tyr Asp Gly Tyr Leu Ala Lys Asp Gly
      50           55           60

Ser Lys Phe Tyr Cys Ser Arg Thr Gln Asn Glu Gly His Pro Lys Trp
      65           70           75           80

Phe Val Leu Gly Val Gly Gln Val Ile Lys Gly Leu Asp Ile Ala Met
      85           90           95

Thr Asp Met Cys Pro Gly Glu Lys Arg Lys Val Val Ile Pro Pro Ser
      100          105          110

Phe Ala Tyr Gly Lys Glu Gly Tyr Ala Glu Gly Lys Ile Pro Pro Asp
      115          120          125

Ala Thr Leu Ile Phe Glu Ile Glu Leu Tyr Ala Val Thr Lys Gly Pro
      130          135          140

Arg Ser Ile Glu Thr Phe Lys Gln Ile Asp Met Asp Asn Asp Arg Gln
      145          150          155          160

Leu Ser Lys Ala Glu Ile Asn Leu Tyr Leu Gln Arg Glu Phe Glu Lys
      165          170          175

Asp Glu Lys Pro Arg Asp Lys Ser Tyr Gln Asp Ala Val Leu Glu Asp
      180          185          190

Ile Phe Lys Lys Asn Asp His Asp Gly Asp Gly Phe Ile Ser Pro Lys
      195          200          205

Glu Tyr Asn Val Tyr Gln His Asp Glu Leu Xaa
      210          215

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<210> 272

<211> 50

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

181

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (50)

<223> Xaa equals stop translation

<400> 272

Met	Trp	Val	Ile	Arg	Val	Phe	Gln	Lys	Thr	Phe	Leu	Phe	Phe	Val	Leu
1					5				10					15	

Phe	Trp	Ser	Val	His	Cys	Ile	Ser	Asp	Lys	Phe	Gly	Cys	Leu	Trp	His
			20					25					30		

Val	Cys	Met	Lys	Arg	Glu	Gly	Asp	Xaa	Asn	Cys	Leu	Ser	Phe	Ser	Xaa
		35					40					45			

Leu	Xaa
	50

<210> 273

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (20)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (122)

<223> Xaa equals stop translation

<400> 273

Met	Pro	Ser	Gln	Thr	Glu	Xaa	Phe	Ala	Ala	Cys	Gly	Gly	His	Ser	Leu
1				5					10					15	

Leu	Leu	Val	Xaa	Leu	Pro	Leu	Gly	Leu	Pro	Phe	Cys	Pro	Arg	Ala	Ala
			20					25					30		

Leu	Cys	Asp	Leu	Pro	Phe	Ser	Leu	Pro	Ser	Phe	Pro	Gly	Gln	Ala	Arg
		35					40					45			

Arg	Gly	Gly	Ala	Glu	Lys	Gln	Gly	Ala	Glu	Gly	Arg	Gly	Leu	Gln	Val
			50			55					60				

Lys	Pro	Arg	Gly	Gln	Arg	Thr	Phe	Gln	Val	Ser	Arg	Thr	Ala	Pro	Ala
65					70					75				80	

182

Ala Pro Arg Ser Arg Gln Pro Arg Pro Pro Ala Ala Leu Pro Ala Leu
 85 90 95

Gly Phe Gly Gly Arg Gly Val Ala Lys Gly Arg Phe Leu Cys Phe Trp
 100 105 110

Cys Leu Tyr Met Leu Arg Ile Asp Gln Xaa
 115 120

<210> 274

<211> 88

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (88)

<223> Xaa equals stop translation

<400> 274

Met Thr Ala Phe Cys Ser Leu Leu Leu Gln Ala Gln Ser Leu Leu Pro
 1 5 10 15

Arg Thr Met Ala Ala Pro Gln Asp Ser Leu Arg Pro Gly Glu Glu Asp
 20 25 30

Glu Gly Met Gln Leu Leu Gln Thr Lys Asp Ser Met Ala Lys Gly Ala
 35 40 45

Arg Pro Gly Ala Xaa Arg Gly Arg Ala Arg Trp Gly Leu Ala Tyr Thr
 50 55 60

Leu Leu His Asn Pro Thr Leu Gln Val Phe Arg Lys Thr Ala Leu Leu
 65 70 75 80

Gly Ala Asn Gly Ala Gln Pro Xaa
 85

<210> 275

<211> 26

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (26)

<223> Xaa equals stop translation

<400> 275

Met Ile Gln Val Ser Val Pro Leu Leu Thr Ile Met Ile Phe Leu Leu

183

1 5 10 15
 Tyr Leu Gln Ile Gly Pro Gly Lys Leu Xaa
 20 25

<210> 276
 <211> 29
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (29)
 <223> Xaa equals stop translation

<400> 276
 Met Leu Leu Asp Pro Phe Ile Leu Leu Phe Cys Leu Phe Ser Thr Ala
 1 5 10 15

Ala Gln Ser Cys Leu Glu Phe Ile Tyr Ile Gln Phe Xaa
 20 25

<210> 277
 <211> 44
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (14)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (44)
 <223> Xaa equals stop translation

<400> 277
 Met Lys Phe Leu Ser Ile Leu Leu Asp Asp Asn Asn Phe Xaa Leu Met
 1 5 10 15

Leu Met Leu Ala Pro Phe Gly Cys Leu Ala Phe Glu Arg Ser Met Lys
 20 25 30

Met Arg Asn Gly Ala Leu Gly Leu Glu Glu Val Xaa
 35 40

<210> 278
 <211> 363
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (307)

184

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (363)

<223> Xaa equals stop translation

<400> 278

Met	Arg	Thr	Leu	Phe	Asn	Leu	Leu	Trp	Leu	Ala	Leu	Ala	Cys	Ser	Pro	1	5	10	15
Val	His	Thr	Thr	Leu	Ser	Lys	Ser	Asp	Ala	Lys	Lys	Ala	Ala	Ser	Lys	20	25	30	
Thr	Leu	Leu	Glu	Lys	Ser	Gln	Phe	Ser	Asp	Lys	Pro	Val	Gln	Asp	Arg	35	40	45	
Gly	Leu	Val	Val	Thr	Asp	Leu	Lys	Ala	Glu	Ser	Val	Val	Leu	Glu	His	50	55	60	
Arg	Ser	Tyr	Cys	Ser	Ala	Lys	Ala	Arg	Asp	Arg	His	Phe	Ala	Gly	Asp	65	70	75	80
Val	Leu	Gly	Tyr	Val	Thr	Pro	Trp	Asn	Ser	His	Gly	Tyr	Asp	Val	Thr	85	90	95	
Lys	Val	Phe	Gly	Ser	Lys	Phe	Thr	Gln	Ile	Ser	Pro	Val	Trp	Leu	Gln	100	105	110	
Leu	Lys	Arg	Arg	Gly	Arg	Glu	Met	Phe	Glu	Val	Thr	Gly	Leu	His	Asp	115	120	125	
Val	Asp	Gln	Gly	Trp	Met	Arg	Ala	Val	Arg	Lys	His	Ala	Lys	Gly	Leu	130	135	140	
His	Ile	Val	Pro	Arg	Leu	Phe	Glu	Asp	Trp	Thr	Tyr	Asp	Asp	Phe	145	150	155	160	
Arg	Asn	Val	Leu	Asp	Ser	Glu	Asp	Glu	Ile	Glu	Glu	Leu	Ser	Lys	Thr	165	170	175	
Val	Val	Gln	Val	Ala	Lys	Asn	Gln	His	Phe	Asp	Gly	Phe	Val	Val	Glu	180	185	190	
Val	Trp	Asn	Gln	Leu	Leu	Ser	Gln	Lys	Arg	Val	Thr	Asp	Gln	Leu	Gly	195	200	205	
Met	Phe	Thr	His	Lys	Glu	Phe	Glu	Gln	Leu	Ala	Pro	Val	Leu	Asp	Gly	210	215	220	
Phe	Ser	Leu	Met	Thr	Tyr	Asp	Tyr	Ser	Thr	Ala	His	Gln	Pro	Gly	Pro	225	230	235	240
Asn	Ala	Pro	Leu	Ser	Trp	Val	Arg	Ala	Cys	Val	Gln	Val	Leu	Asp	Pro	245	250	255	
Lys	Ser	Lys	Trp	Arg	Ser	Lys	Ile	Leu	Leu	Gly	Leu	Asn	Phe	Tyr	Gly	260	265	270	

185

Met Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala
 275 280 285

Arg Tyr Ile Gln Thr Leu Lys Asp His Arg Pro Arg Met Val Trp Asp
 290 295 300

Ser Gln Xaa Ser Glu His Phe Phe Glu Tyr Lys Lys Ser Arg Ser Gly
 305 310 315 320

Arg His Val Val Phe Tyr Pro Thr Leu Lys Ser Leu Gln Val Arg Leu
 325 330 335

Glu Leu Ala Arg Glu Leu Gly Val Gly Val Ser Ile Trp Glu Leu Gly
 340 345 350

Gln Gly Leu Asp Tyr Phe Tyr Asp Leu Leu Xaa
 355 360

<210> 279
 <211> 128
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (128)
 <223> Xaa equals stop translation

<400> 279
 Leu Pro Thr Lys Ile Leu Val Lys Pro Asp Arg Thr Phe Glu Ile Lys
 1 5 10 15

Ile Gly Gln Pro Thr Val Ser Tyr Phe Leu Lys Ala Ala Ala Gly Ile
 20 25 30

Glu Lys Gly Ala Arg Gln Thr Gly Lys Glu Val Ala Gly Leu Val Thr
 35 40 45

Leu Lys His Val Tyr Glu Ile Ala Arg Ile Lys Ala Gln Asp Glu Ala
 50 55 60

Phe Ala Leu Gln Asp Val Pro Leu Ser Ser Val Val Arg Ser Ile Ile
 65 70 75 80

Gly Ser Ala Arg Ser Leu Gly Ile Arg Val Val Lys Asp Leu Ser Ser
 85 90 95

Glu Glu Leu Ala Ala Phe Gln Lys Glu Arg Ala Ile Phe Leu Ala Ala
 100 105 110

Gln Lys Glu Ala Asp Leu Ala Ala Gln Glu Glu Ala Ala Lys Lys Xaa
 115 120 125

186

<210> 280
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (54)
<223> Xaa equals stop translation

<400> 280
Met Leu Leu Gln Ile His Pro Leu Leu Pro Ser Pro Thr Ile Pro His
1 5 10 15
Ile Leu Leu Leu Phe Leu Tyr Pro Thr Phe Ser Ile Leu Glu His Ser
20 25 30
Cys Ser Tyr Cys Ile Glu Tyr Leu Trp Val Cys Leu Leu Phe Cys Leu
35 40 45
Ser Leu Trp Phe Leu Xaa
50

<210> 281
<211> 29
<212> PRT
<213> Homo sapiens

<400> 281
Met Cys Leu Trp Cys Cys Gly Asp Val Cys Ser Gly Leu Ser Ser Leu
1 5 10 15
Leu Ser Leu Cys Val Cys Cys Val Val Leu Ala Val Cys
20 25

<210> 282
<211> 26
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (26)
<223> Xaa equals stop translation

<400> 282
Glu Gly Leu Arg Leu Leu Leu Ser Leu Pro Ala Ala Leu Pro Arg Ser
1 5 10 15
Cys Cys His Pro Arg Trp Leu Pro Val Xaa
20 25

<210> 283
<211> 221

187

<212> PRT

<213> Homo sapiens

<400> 283

```

Met Phe His Gly Ile Pro Ala Thr Pro Gly Ile Gly Ala Pro Gly Asn
 1           5           10           15

Lys Pro Glu Leu Tyr Glu Glu Val Lys Leu Tyr Lys Asn Ala Arg Glu
          20           25           30

Arg Glu Lys Tyr Asp Asn Met Ala Glu Leu Phe Ala Val Val Lys Thr
          35           40           45

Met Gln Ala Leu Glu Lys Ala Tyr Ile Lys Asp Cys Val Ser Pro Ser
          50           55           60

Glu Tyr Thr Ala Ala Cys Ser Arg Leu Leu Val Gln Tyr Lys Ala Ala
 65           70           75           80

Phe Arg Gln Val Gln Gly Ser Glu Ile Ser Ser Ile Asp Glu Phe Cys
          85           90           95

Arg Lys Phe Arg Leu Asp Cys Pro Leu Ala Met Glu Arg Ile Lys Glu
          100          105          110

Asp Arg Pro Ile Thr Ile Lys Asp Asp Lys Gly Asn Leu Asn Arg Cys
          115          120          125

Ile Ala Asp Val Val Ser Leu Phe Ile Thr Val Met Asp Lys Leu Arg
          130          135          140

Leu Glu Ile Arg Ala Met Asp Glu Ile Gln Pro Asp Leu Arg Glu Leu
          145          150          155          160

Met Glu Thr Met His Arg Met Ser His Leu Pro Pro Asp Phe Glu Gly
          165          170          175

Arg Gln Thr Val Ser Gln Trp Leu Gln Thr Leu Ser Gly Met Ser Ala
          180          185          190

Ser Asp Glu Leu Asp Asp Ser Gln Val Arg Gln Met Leu Phe Asp Leu
          195          200          205

Glu Ser Ala Tyr Asn Ala Phe Asn Arg Phe Leu His Ala
          210          215          220

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<210> 284

<211> 40

<212> PRT

<213> Homo sapiens

<400> 284

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Met Gly Asn Ser Gln Val Pro Gln Ser Ser Asp Phe Ser Ser Ile Leu
 1           5           10           15

Leu Thr Thr Ser Leu Gly Thr Tyr Ser Leu Leu Leu Gly Thr Ala Gly
          20           25           30

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188

Ala Arg Thr Gly Ser Pro Met Ser
 35 40

<210> 285
 <211> 49
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (6)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (38)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (49)
 <223> Xaa equals stop translation

<400> 285
 Met Gln Ala Pro Phe Xaa His Phe Ser Phe Arg Met Phe Ser Asn Leu
 1 5 10 15
 Tyr Cys Phe Ser Asp Phe Gln Pro Asn Ile Ser Pro Cys Pro Leu Cys
 20 25 30
 His Cys Ile Leu Pro Xaa His His His Val Phe Leu Leu Leu Ala Val
 35 40 45

Xaa

<210> 286
 <211> 52
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (52)
 <223> Xaa equals stop translation

<400> 286
 Met Lys Leu Val Thr Met Phe Asp Lys Leu Ser Arg Asn Arg Val Ile
 1 5 10 15
 Gln Pro Met Gly Met Ser Pro Arg Gly His Leu Thr Ser Leu Gln Asp
 20 25 30
 Ala Met Cys Glu Thr Met Glu Gln Gln Leu Ser Ser Asp Pro Asp Ser
 35 40 45

189

Asp Pro Asp Xaa
50

<210> 287
<211> 32
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (32)
<223> Xaa equals stop translation

<400> 287
Met Ala Val Gly Glu Ala Val Phe Val Pro Leu Gln His Pro Pro Leu
1 5 10 15
Leu His Gly Ser Pro Ile Pro Lys Leu Leu Pro Gly Pro Leu Leu Xaa
20 25 30

<210> 288
<211> 57
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (52)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (57)
<223> Xaa equals stop translation

<400> 288
Met Asn Gly Cys His Arg Arg Lys Arg Leu His Leu Cys Lys Thr Ile
1 5 10 15
Tyr Leu Leu Trp Phe Val Phe Ser Phe Leu Leu Ser Asn Glu Val Val
20 25 30
Ser Ser His Trp His Ile Leu Arg Ala Val Gln Ile Ile Cys Thr Leu
35 40 45
Phe His Arg Xaa Ile Ser Ala Phe Xaa
50 55

<210> 289
<211> 22
<212> PRT

190

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals stop translation

<400> 289

Met	Gly	Trp	Val	Ser	Ser	Pro	His	Val	Lys	Arg	Arg	Glu	Cys	Val	Leu
1				5					10					15	

Lys	Lys	Pro	Phe	Phe	Xaa
			20		

<210> 290

<211> 51

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> Xaa equals stop translation

<400> 290

Met	Phe	Asn	Phe	Phe	Lys	Asn	Pro	Leu	Leu	Thr	Cys	Leu	Phe	Ile	Ser
1				5					10					15	

Cys	Tyr	Leu	Tyr	Leu	Ser	Leu	Leu	Val	Asn	Lys	Val	Leu	Phe	Ala	Glu
		20						25						30	

Glu	Gly	Leu	Cys	Cys	Thr	Tyr	Cys	Thr	Thr	Ser	Asn	Thr	Gly	Glu	Gly
		35					40						45		

Gly	Val	Xaa
		50

<210> 291

<211> 98

<212> PRT

<213> Homo sapiens

<400> 291

Met	Val	Tyr	Ile	Tyr	His	Ile	Phe	Phe	Ile	His	Ser	Leu	Leu	Asp	Gly
1				5					10					15	

Gln	Leu	Gly	Trp	Phe	His	Ile	Phe	Ala	Ile	Val	Ser	Cys	Ala	Ala	Pro
		20						25						30	

Asp	Ile	Ile	Phe	Asn	Ser	Phe	Ala	Phe	Ser	Thr	Tyr	Ile	Ser	Lys	Ser
		35					40						45		

Cys	Ser	Phe	Tyr	Leu	Gln	Asn	Val	Ser	Cys	Ile	His	Ser	Ser	Leu	Ser
		50				55					60				

Ile	Phe	Asn	Leu	Phe	Gln	Cys	Pro	Ile	Ile	Ser	Cys	Met	Glu	Glu	Cys
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

191

65		70		75		80									
Asn	Asn	Trp	Leu	Thr	Gly	Leu	Phe	Leu	His	Phe	Lys	Ile	Lys	Arg	Cys
			85						90					95	

Asp Arg

<210> 292

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (66)

<223> Xaa equals stop translation

<400> 292

Met	Leu	Cys	Thr	Ile	Leu	Thr	Val	Val	Ile	Ile	Ile	Ala	Ala	Gln	Thr
1				5					10					15	

Thr	Arg	Thr	Thr	Gly	Ile	Pro	Lys	Asn	Ala	Pro	Gly	Pro	Ala	Pro	Leu
				20				25					30		

Cys	Ala	Pro	Arg	Ser	Pro	Arg	Leu	Phe	Leu	Gln	Xaa	Tyr	Arg	Gly	Pro
		35					40					45			

Asn	Gly	Arg	Pro	Ala	His	Pro	Phe	Leu	Gly	Pro	Ser	Asp	Leu	Asp	Thr
	50						55				60				

Ser Xaa

65

<210> 293

<211> 257

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (187)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (229)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (232)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (236)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (237)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (257)

<223> Xaa equals stop translation

<400> 293

Met	Leu	Gly	Ala	Lys	Pro	His	Trp	Leu	Pro	Gly	Pro	Leu	His	Ser	Pro
1				5					10					15	

Gly	Leu	Pro	Leu	Val	Leu	Val	Leu	Leu	Ala	Leu	Gly	Ala	Gly	Trp	Ala
		20						25					30		

Gln	Glu	Gly	Ser	Glu	Pro	Val	Leu	Leu	Glu	Gly	Glu	Cys	Leu	Val	Val
		35					40					45			

Cys	Glu	Pro	Gly	Arg	Ala	Ala	Ala	Gly	Gly	Pro	Gly	Gly	Ala	Ala	Leu
	50				55					60					

Gly	Glu	Ala	Pro	Pro	Gly	Arg	Val	Ala	Phe	Xaa	Ala	Val	Arg	Ser	His
65					70				75						80

His	His	Glu	Pro	Ala	Gly	Glu	Thr	Gly	Asn	Gly	Thr	Ser	Gly	Ala	Ile
			85						90					95	

Tyr	Phe	Asp	Gln	Val	Leu	Val	Asn	Glu	Gly	Gly	Gly	Phe	Asp	Arg	Ala
		100						105					110		

Ser	Gly	Ser	Phe	Val	Ala	Pro	Val	Arg	Gly	Val	Tyr	Ser	Phe	Arg	Phe
	115						120					125			

His	Val	Val	Lys	Val	Tyr	Asn	Arg	Gln	Thr	Val	Gln	Val	Ser	Leu	Met
	130					135					140				

Leu	Asn	Thr	Trp	Pro	Val	Ile	Ser	Ala	Phe	Ala	Asn	Asp	Pro	Asp	Val
145					150					155					160

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<210> 294
<211> 103
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (78)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (80)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (81)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (82)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (103)
<223> Xaa equals stop translation
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<400> 294
Met Ala Pro Arg Ala Leu Pro Gly Ser Ala Val Leu Ala Ala Ala Val
1 5 10 15

Phe Val Gly Gly Ala Val Ser Ser Pro Leu Val Ala Pro Asp Asn Gly

20

25

30

Ile Glu Glu Glu Lys Gly Xaa
100

Xaa

Met Val Leu Gly Leu Leu Leu Leu Leu Xaa Phe Phe Ser Phe Ser Ser
1 5 10 15

195

Ser Pro Ser Pro Ser Ser Ser Leu Leu Leu Leu Ser Ser Phe Phe Phe
 20 25 30

Gln Ser Leu Ala Leu Ser Pro Arg Leu Glu Xaa
 35 40

<210> 297
 <211> 21
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (21)
 <223> Xaa equals stop translation

<400> 297
 Glu Trp Leu Val Phe Thr Phe Leu Leu Val Phe Gly Ser Pro Leu Gly
 1 5 10 15

Lys Gly Pro Leu Xaa
 20

<210> 298
 <211> 70
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (70)
 <223> Xaa equals stop translation

<400> 298
 Met Ile Arg Ala Leu Ser Leu Phe Leu Leu Ile Phe Asp Ala Ala Leu
 1 5 10 15

Phe Ser Leu Ser Val Phe Val Phe Ile Gly His Leu Leu Pro Met Pro
 20 25 30

Lys Gly Thr Gly Leu His Ser Cys Ala Lys His Leu Ile Lys Ser Leu
 35 40 45

Lys Glu Asn Val Leu Pro Leu Met Asn Tyr Pro Asp Cys Lys Leu Lys
 50 55 60

Ile Asn Ile Ser Pro Xaa
 65 70

<210> 299
 <211> 75
 <212> PRT
 <213> Homo sapiens

<220>

196

<221> SITE

<222> (75)

<223> Xaa equals stop translation

<400> 299

Met Gly Lys Leu Ile Arg Leu Ser Val Met Val Met Ser Val Arg Arg
 1 5 10 15

Leu Phe Ser Ile Tyr Trp Val Leu Ser Thr Val Pro Asp Ala Val Gly
 20 25 30

Ser Arg Gly Gly Met Glu Glu Glu Cys Ser Arg Gly Leu Cys Cys Val
 35 40 45

Ala Gly Gln His Lys Gln Ala Lys Gly Lys Arg Gln Ala Trp Asn Lys
 50 55 60

Gly Gly Glu Tyr Gln Cys Val Thr Tyr Cys Xaa
 65 70 75

<210> 300

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals stop translation

<400> 300

Met Pro Ala Leu Val Thr Leu Leu Leu Leu Phe Pro Leu Leu Pro Leu
 1 5 10 15

Met Glu Ala Ser Cys His Val Met Arg Cys Pro Met Glu Arg Pro Thr
 20 25 30

Xaa

<210> 301

<211> 17

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (17)

<223> Xaa equals stop translation

<400> 301

Glu Ala Pro Trp Gly Leu Leu Lys Leu Leu Leu Leu Ala Val Phe
 1 5 10 15

Xaa

197

<210> 302
 <211> 17
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals stop translation

<400> 302
 Met Gln Gln Lys Gln Lys Lys Ala Asn Glu Lys Lys Glu Glu Pro Lys
 1 5 10 15

Xaa

<210> 303
 <211> 111
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (9)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 303
 Met Gln Ser Pro Lys Phe Leu Ser Xaa Thr Pro Tyr Leu Phe Gln Thr
 1 5 10 15

Pro Phe His Leu Ile Ser Leu Pro Cys His Phe Phe Ile Phe Lys Met
 20 25 30

Pro Ile Val Tyr Val Leu Phe Lys Phe Phe Glu Arg Leu Lys Gln Pro
 35 40 45

Leu Ser Lys Ile Pro Phe Cys Leu Leu Ala Phe Lys Phe Ser Ile Arg
 50 55 60

Ala Phe Phe Leu Pro Leu Trp His Ala Ala Leu Trp Leu Ser Phe Val
 65 70 75 80

Phe Phe Ala Gly Phe Leu His Asp Val Val Val Val Ser Cys Leu Thr
 85 90 95

Leu Cys Gly Val Val Ser Cys Ser Phe Ser Ser Pro Arg Cys Leu
 100 105 110

<210> 304
 <211> 12
 <212> PRT
 <213> Homo sapiens

198

<220>
<221> SITE
<222> (12)
<223> Xaa equals stop translation

<400> 304
Met Ala Leu Leu Ile Ser Ser Leu Ile Trp Ser Xaa
1 5 10

<210> 305
<211> 35
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (35)
<223> Xaa equals stop translation

<400> 305
Met Gln Met Phe Thr Val Ser Leu Leu Leu Ser Leu Leu Leu Arg Ser
1 5 10 15
Thr Asp Gln Asn His Leu Gln Leu Leu Val Gly Arg Glu Asp His Tyr
20 25 30

Gly Gly Xaa
35

<210> 306
<211> 15
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (15)
<223> Xaa equals stop translation

<400> 306
Met Ser Glu Ser Ala Cys Ile Leu Asn Asn Gln Lys Glu Leu Xaa
1 5 10 15

<210> 307
<211> 44
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (44)
<223> Xaa equals stop translation

<400> 307
Met Asp Leu Asp Arg Val Lys Ala Glu Ala Thr Glu Asp Ile Thr Ser

199

1 5 10 15
 Gly Val Leu Cys Leu Leu Phe Leu Arg Leu Pro Pro Asn Ser Cys Ile
 20 25 30
 Phe Pro Ser Ala Val Leu Gly Ser Thr Arg Thr Xaa
 35 40

<210> 308
 <211> 137
 <212> PRT
 <213> Homo sapiens

<400> 308
 Met Met Val Val Gly Thr Gly Thr Ser Leu Ala Leu Ser Ser Leu Leu
 1 5 10 15
 Ser Leu Leu Leu Phe Ala Gly Met Gln Met Tyr Ser Arg Gln Leu Ala
 20 25 30
 Ser Thr Glu Trp Leu Thr Ile Gln Gly Gly Leu Leu Gly Ser Gly Leu
 35 40 45
 Phe Val Phe Ser Leu Thr Ala Phe Asn Asn Leu Glu Asn Leu Val Phe
 50 55 60
 Gly Lys Gly Phe Gln Ala Lys Ile Phe Pro Glu Ile Leu Leu Cys Leu
 65 70 75 80
 Leu Leu Ala Leu Phe Ala Ser Gly Leu Ile His Arg Val Cys Val Thr
 85 90 95
 Thr Cys Phe Ile Phe Ser Met Val Gly Leu Tyr Tyr Ile Asn Lys Ile
 100 105 110
 Ser Ser Thr Leu Tyr Gln Ala Ala Ala Pro Val Leu Thr Pro Ala Lys
 115 120 125
 Val Thr Gly Lys Ser Lys Lys Arg Asn
 130 135

<210> 309
 <211> 34
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals stop translation

<400> 309
 Met Phe Ile Phe Leu Phe Leu Cys Val Leu Ser Arg Lys Ile Gln Glu
 1 5 10 15
 Glu Tyr Tyr Arg Leu Phe Lys Asn Val Pro Cys Cys Phe Gly Cys Leu

200

20

25

30

Arg Xaa

<210> 310

<211> 137

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (137)

<223> Xaa equals stop translation

<400> 310

Met	Arg	Thr	Pro	Gly	Pro	Leu	Pro	Val	Leu	Leu	Leu	Leu	Ala	Gly
1				5				10					15	

Ala	Pro	Ala	Ala	Arg	Pro	Thr	Pro	Pro	Thr	Cys	Tyr	Ser	Arg	Met	Arg
			20					25					30		

Ala	Leu	Ser	Gln	Glu	Ile	Thr	Arg	Asp	Phe	Asn	Leu	Leu	Gln	Val	Ser
		35					40					45			

Glu	Pro	Ser	Glu	Pro	Cys	Val	Arg	Tyr	Leu	Pro	Arg	Leu	Tyr	Leu	Asp
	50					55					60				

Ile	His	Asn	Tyr	Cys	Val	Leu	Asp	Lys	Leu	Arg	Asp	Phe	Val	Ala	Ser
65					70					75					80

Pro	Pro	Cys	Trp	Lys	Val	Ala	Gln	Val	Asp	Ser	Leu	Lys	Asp	Lys	Ala
			85						90					95	

Arg	Lys	Leu	Tyr	Thr	Ile	Met	Asn	Ser	Phe	Cys	Arg	Arg	Asp	Leu	Val
		100						105					110		

Phe	Leu	Leu	Asp	Asp	Cys	Asn	Ala	Leu	Glu	Tyr	Pro	Ile	Pro	Val	Thr
		115					120					125			

Thr	Val	Leu	Pro	Asp	Arg	Gln	Arg	Xaa
	130					135		

<210> 311

<211> 58

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

201

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (58)

<223> Xaa equals stop translation

<400> 311

Met	Trp	Leu	Leu	Lys	Pro	Ser	Ala	His	Ser	Pro	Val	His	Xaa	Leu	Val
1				5					10					15	

Leu	Leu	Phe	Pro	Arg	Gly	Trp	Ser	Gln	Pro	Gly	Thr	His	Lys	Arg	Gln
			20					25					30		

Ile	Leu	Val	Asn	Xaa	Ala	Ser	Leu	Pro	Gly	Gly	Cys	Leu	Leu	Pro	Trp
		35					40					45			

Ile	Trp	Ser	Gly	Ala	Ala	Leu	Arg	Phe	Xaa
	50					55			

<210> 312

<211> 35

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals stop translation

<400> 312

Met	Ser	Arg	Arg	Ala	Glu	Ala	Ser	Ile	Phe	Val	Leu	Pro	Lys	Thr	Leu
1				5					10					15	

Leu	Phe	Val	Leu	Phe	Pro	Ala	Phe	Pro	Ser	Pro	Ala	Val	Gly	Cys	Pro
			20					25					30		

Val	Pro	Xaa
	35	

<210> 313

<211> 90

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 313

Met	Ala	Leu	Glu	Met	Val	Trp	Gly	Ser	Val	Tyr	His	Cys	Ser	Cys	Tyr
1				5					10					15	

Ile	Thr	Pro	Trp	Ser	Lys	Ile	Gln	Ser	Phe	Ser	Leu	Ser	Leu	Phe	Gln
		20						25					30		

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<210> 314
<211> 95
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (95)
<223> Xaa equals stop translation
```

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<400> 314
Met Phe Val Leu Phe Ser Leu Pro Lys Tyr Ala Gly Leu Arg Leu Pro
  1             5             10             15

Ile Pro Gly Leu Ser Ala Leu Leu Val Phe Leu Leu Ser Leu Phe Ser
      20             25             30

Arg Arg Ala Gln Val Glu Leu Thr Thr Gly Arg Glu Thr Leu Pro Lys
      35             40             45

Asn Leu Gln Gly Tyr Phe Pro Glu Phe Gly Phe Gln Val Gln Asn Phe
      50             55             60

Leu Ser Cys Lys Ile Tyr Ala Ala Ser Gln Lys Gln Pro Leu Pro Pro
  65             70             75             80

Leu Tyr Gln Leu Arg Phe Tyr Leu Lys His Met Gly Leu Pro Xaa
      85             90             95

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<210> 315
<211> 44
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (44)
<223> Xaa equals stop translation
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<400> 315
Met Ser Ser His Trp Thr Leu Lys Ile Leu Leu Val Pro Leu Phe Tyr
1 5 10 15

203

Leu Ser Leu Glu Phe Pro Ser Gly Phe Val Leu Cys Leu Ala Asn Asp
 20 25 30

Leu Gly Tyr His Phe Ser Ser Arg Val Arg Ser Xaa
 35 40

<210> 316
 <211> 31
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals stop translation

<400> 316
 Met Leu Val Val Asn Ile Asn Leu Val Phe Leu Leu Phe Phe Ile Phe
 1 5 10 15

Leu Cys Tyr Leu Asp Ala Cys Ile Asn Val Phe Cys Phe Tyr Xaa
 20 25 30

<210> 317
 <211> 113
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (69)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (113)
 <223> Xaa equals stop translation

<400> 317
 Met Pro Val Leu Pro Gly Arg Thr Thr Ala Leu Leu Ser Leu Thr Leu
 1 5 10 15

Ala Phe Ala Val Pro Cys Ser Gly Val Glu Ala Gly Pro Cys Val Pro
 20 25 30

Arg Ser His Gly Cys Ser Ser Trp Glu Ala Ser Val Cys Val Thr Ser
 35 40 45

Ser Thr Pro Gly Gly Ser Trp Arg Ala Arg Ala Leu Phe Pro Ser Ala
 50 55 60

Ala Trp His Arg Xaa Ala Ala Trp Asp Ser Pro Trp Thr Gln Thr Gly
 65 70 75 80

Asp Phe Ala Arg Gly Ala Met Gly Gly Ala Gly Ala Leu Pro Gly Gly
 85 90 95

204

Cys Val Cys Ile Ser Gly Arg Pro Arg Ala Gln Lys Leu Pro Ala Leu
 100 105 110

Xaa

<210> 318

<211> 235

<212> PRT

<213> Homo sapiens

<400> 318

Met Ser Pro Arg Tyr Pro Gly Gly Pro Arg Pro Pro Leu Arg Ile Pro
 1 5 10 15

Asn Gln Ala Leu Gly Gly Val Pro Gly Ser Gln Pro Leu Leu Pro Ser
 20 25 30

Gly Met Asp Pro Thr Arg Gln Gln Gly His Pro Asn Met Gly Gly Pro
 35 40 45

Met Gln Arg Met Thr Pro Pro Arg Gly Met Val Pro Leu Gly Pro Gln
 50 55 60

Asn Tyr Gly Gly Ala Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro
 65 70 75 80

Gly Met Pro Gly Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro
 85 90 95

Asn Pro Thr Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly
 100 105 110

Asn Tyr Val Gly Pro Pro Gly Gly Gly Gly Pro Pro Gly Thr Pro Ile
 115 120 125

Met Pro Ser Pro Ala Asp Ser Thr Asn Ser Gly Asp Asn Met Tyr Thr
 130 135 140

Leu Met Asn Ala Val Pro Pro Gly Pro Asn Arg Pro Asn Phe Pro Met
 145 150 155 160

Gly Pro Gly Ser Asp Gly Pro Met Gly Gly Leu Gly Gly Met Glu Ser
 165 170 175

His His Met Asn Gly Ser Leu Gly Ser Gly Asp Met Asp Ser Ile Ser
 180 185 190

Lys Asn Ser Pro Asn Asn Met Ser Leu Ser Asn Gln Pro Gly Thr Pro
 195 200 205

Arg Asp Asp Gly Glu Met Gly Gly Asn Phe Leu Asn Pro Phe Gln Ser
 210 215 220

Glu Ser Tyr Ser Pro Ser Met Thr Met Ser Val
 225 230 235

205

<210> 319
<211> 35
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (35)
<223> Xaa equals stop translation

<400> 319
Met Glu Asn Phe Phe Phe Ser Phe Tyr Leu Phe Leu Ile Thr Leu Ile
1 5 10 15

Pro Asn Gly Arg Thr Leu Ser Thr Thr Ala Asp His Cys Lys Ile Pro
20 25 30

Cys Ile Xaa
35

<210> 320
<211> 35
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (35)
<223> Xaa equals stop translation

<400> 320
Met Glu Leu Trp Glu Leu Ala Leu Cys Leu Leu Val Ala Leu Ser Ala
1 5 10 15

His Met Phe Thr Val Gln Leu Leu Ala Asp Leu Gly Phe Leu Phe Gly
20 25 30

Gly Phe Xaa
35

<210> 321
<211> 82
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (82)
<223> Xaa equals stop translation

<400> 321
Met Gly Ala Gly Ile Leu Ala Leu Leu Leu Pro Leu Glu Ser Val Leu
1 5 10 15

206

Thr Cys Ser Trp Ile Ser Val Ser Thr Ser Glu Arg Gln Leu Trp Gln
 20 25 30

Ser Ser Gln Lys Ala Thr Ile Leu Ser Leu Lys Leu Asp Ser Cys Phe
 35 40 45

Cys Gly His Ser Gly Leu Lys Gly Lys Asn Glu Asp Thr Asp Ser Ser
 50 55 60

Val Pro Ile Ile Pro Ser Lys Thr His Thr His Leu Gly Lys His Leu
 65 70 75 80

Ile Xaa

<210> 322
 <211> 72
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (47)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (70)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (72)
 <223> Xaa equals stop translation

<400> 322
 Met Phe Tyr Phe Val Leu Phe Ile Tyr Ser Ser Ser Glu Thr Trp Ser
 1 5 10 15

Gly Ser Val Ala Gln Asp Gly Val His Gly Val Ile Ile Gly His Cys
 20 25 30

Ser Val Glu Leu Pro Gly Ser Gly Asp Pro Pro Ala Ser Ala Xaa Leu
 35 40 45

Val Ala Gly Thr Ile Gly Thr Cys Pro Thr Met Pro Gly Phe Val Tyr
 50 55 60

Phe Leu Asn Asp Val Xaa Asn Xaa
 65 70

<210> 323
 <211> 34
 <212> PRT
 <213> Homo sapiens

207

<220>
 <221> SITE
 <222> (10)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (34)
 <223> Xaa equals stop translation

 <400> 323
 Met Asp Ser Thr Leu Arg Gln Gly Arg Xaa Leu Leu Thr Leu Val Pro
 1 5 10 15
 Ala Ser Leu Phe Ser Leu Thr Leu Gly Gly Pro Gly Pro Trp Lys Asp
 20 25 30

 Pro Xaa

 <210> 324
 <211> 115
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (111)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (112)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (115)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 324
 Met Gln Val Val Gly Ser Trp Pro Gly Arg Val Gly Val Val Gly Leu
 1 5 10 15
 Ala Phe Ser Leu Val Ile Pro Pro Pro Ala Ile Cys Ile Ala Gly Pro
 20 25 30
 Ala Pro Gly Leu Gly Gly Gly Glu Arg Gln Gln Lys Gly Leu Gly Arg
 35 40 45
 Gly Gly Gly Gly Leu Arg Asn Cys Pro Gly Arg Val Gly Met Ala Ala
 50 55 60
 Glu Pro Gly Ala Leu Leu Cys Leu Thr Ser Arg Asp Gly Ser Leu Leu
 65 70 75 80
 Leu Ser Cys Val Arg Pro His His Val Ile Lys Pro Lys Gly Thr Ala

208

	85		90		95
Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Xaa Xaa					
	100		105		110

Gly Gly Xaa
115

<210> 325
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (99)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 325
Met Asp Leu Pro Gln Phe Ile Tyr Leu Phe Ile Phe Cys Phe Cys Cys
1 5 10 15

Leu Ala Ile Val Asn Asn Ala Ser Ile Asn Ile His Ile Gln Val Ser
20 25 30

Met Trp Leu Tyr Val Phe Ile Ser Leu Gly Tyr Leu His Gly Ser Arg
35 40 45

Ile Leu Gly His Asn Ile Ile Leu Cys Leu Thr Ser Gln Arg Ile Ala
50 55 60

Lys Arg Phe Phe Ile Val Ala Ala Ser Phe Thr Phe Pro Pro Ala Met
65 70 75 80

Tyr Lys Asp Phe Tyr Phe Ser Ile Ser Leu His Leu Pro Thr Leu Leu
85 90 95

Phe Xaa Xaa Xaa Phe Val Phe Ser Leu Leu Pro Pro
100 105

<210> 326
<211> 65
<212> PRT
<213> Homo sapiens

<220>

209

<221> SITE
 <222> (36)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (65)
 <223> Xaa equals stop translation

 <400> 326
 Met Cys Ser Pro Ser Leu Ser Ser Ser Pro Pro Pro Leu Leu Gln Val
 1 5 10 15
 Phe Phe Phe Phe Phe Phe Ser Pro His Trp Ala Ala Lys Val Val Pro
 20 25 30
 Gln Trp Lys Xaa Arg His Pro Gln Val Ser Ser Gln Leu Leu Leu Cys
 35 40 45
 Phe Leu Arg Val Asn Cys Gln Phe Leu Phe Leu Gln Glu Ile Leu Phe
 50 55 60
 Xaa
 65

 <210> 327
 <211> 49
 <212> PRT
 <213> Homo sapiens

 <400> 327
 Met Cys Leu Ser Arg Trp Lys Ile Phe Tyr Thr Leu Leu Ile Leu Phe
 1 5 10 15
 Ala Phe Phe Ser Ile Thr Ser Glu Asn Glu Thr Phe Tyr Met Ile Ile
 20 25 30
 Ile His His Asn Pro Thr Gln Ile Thr Ala Ser Cys Ser Phe Thr Phe
 35 40 45
 Leu

 <210> 328
 <211> 293
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (36)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 328
 Met Glu Arg Pro Asp Trp Glu Thr Ala Ile Gln Lys Pro Leu Cys Ser
 1 5 10 15

210

Leu Pro Ala Gly Ser Gly Asn Ala Leu Ala Ala Ser Leu Asn His Tyr
 20 25 30
 Ala Gly Tyr Xaa Gln Val Thr Asn Glu Asp Leu Leu Thr Asn Cys Thr
 35 40 45
 Leu Leu Leu Cys Arg Arg Leu Leu Ser Pro Met Asn Leu Leu Ser Leu
 50 55 60
 His Thr Ala Ser Gly Leu Arg Leu Phe Ser Val Leu Ser Leu Ala Trp
 65 70 75 80
 Gly Phe Ile Ala Asp Val Asp Leu Glu Ser Glu Lys Tyr Arg Arg Leu
 85 90 95
 Gly Glu Met Arg Phe Thr Leu Gly Thr Phe Leu Arg Leu Ala Ala Leu
 100 105 110
 Arg Thr Tyr Arg Gly Arg Leu Ala Tyr Leu Pro Val Gly Arg Val Gly
 115 120 125
 Ser Lys Thr Pro Ala Ser Pro Val Val Val Gln Gln Gly Pro Val Asp
 130 135 140
 Ala His Leu Val Pro Leu Glu Glu Pro Val Pro Ser His Trp Thr Val
 145 150 155 160
 Val Pro Asp Glu Asp Phe Val Leu Val Leu Ala Leu Leu His Ser His
 165 170 175
 Leu Gly Ser Glu Met Phe Ala Ala Pro Met Gly Arg Cys Ala Ala Gly
 180 185 190
 Val Met His Leu Phe Tyr Val Arg Ala Gly Val Ser Arg Ala Met Leu
 195 200 205
 Leu Arg Leu Phe Leu Ala Met Glu Lys Gly Arg His Met Glu Tyr Glu
 210 215 220
 Cys Pro Tyr Leu Val Tyr Val Pro Val Val Ala Phe Arg Leu Glu Pro
 225 230 235 240
 Lys Asp Gly Lys Gly Val Phe Ala Val Asp Gly Glu Leu Met Val Ser
 245 250 255
 Glu Ala Val Gln Gly Gln Val His Pro Asn Tyr Phe Trp Met Val Ser
 260 265 270
 Gly Cys Val Glu Pro Pro Pro Ser Trp Lys Pro Gln Gln Met Pro Pro
 275 280 285
 Pro Glu Glu Pro Leu
 290

<210> 329

<211> 68

211

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (68)

<223> Xaa equals stop translation

<400> 329

Met	Pro	Leu	Glu	Gly	Phe	Cys	Leu	Val	Leu	Asp	Ile	Gly	Phe	Leu	Leu
1				5					10					15	

Val	Met	Leu	Ile	Ser	Leu	Ala	Ser	Glu	Cys	Phe	Thr	Thr	Cys	Leu	Asp
			20					25					30		

Ser	Phe	Ser	Thr	Thr	Glu	Pro	Gly	Cys	Lys	Phe	Tyr	Lys	Leu	Leu	His
		35					40					45			

Ser	Val	Ser	Leu	Leu	Asn	Ile	Asn	Phe	Asn	Val	Lys	Ser	Leu	Leu	Cys
		50				55					60				

Ser	His	Ile	Xaa
	65		

<210> 330

<211> 105

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (105)

<223> Xaa equals stop translation

<400> 330

Met	Pro	Leu	Gln	Leu	Ser	Gly	Gln	Tyr	Trp	Ile	Ser	Leu	Leu	Val	Phe
1				5					10					15	

Leu	Ser	Leu	Gln	Pro	Phe	Pro	Gln	Ala	Ala	Ile	Pro	Cys	Ala	Leu	Thr
			20					25					30		

Asp	Val	Gly	Gly	Ser	Cys	Val	Ile	Cys	His	Ile	Leu	Leu	Asn	Cys	Leu
		35					40					45			

Cys	Ile	Leu	Phe	Thr	Leu	Thr	Ala	Pro	Ser	Leu	Ser	His	Val	Leu	Leu
		50				55					60				

Ile	Lys	Met	Ser	Leu	Ser	Val	Cys	Tyr	Glu	Pro	Gly	Ala	Asp	Leu	Ser
	65					70				75				80	

Asp	Arg	Ala	Ala	Thr	Gly	Asn	Lys	Lys	Leu	Thr	Arg	Ser	Thr	Cys	Leu
				85					90					95	

Leu	Met	His	Ser	Asn	Lys	Leu	Cys	Xaa
				100				105

212

<210> 331
<211> 58
<212> PRT
<213> Homo sapiens

<400> 331
Met Trp Gly Cys Ser Gly Leu Gly His Arg Thr Val Ser Phe Leu Leu
1 5 10 15
Leu Leu Pro Cys Ser Phe Pro Arg Pro Cys Gly Leu Phe Gly Leu Ile
20 25 30
Pro Ile Ser Arg Pro Cys Lys Val Glu Ala Pro Arg Pro Leu Ser Pro
35 40 45
Thr Thr Leu Met Cys Gln Ser Pro Leu Leu
50 55

<210> 332
<211> 39
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (14)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (39)
<223> Xaa equals stop translation

<400> 332
Met Leu Asn Val Leu Ser Lys Val Gln Gln Leu Val Ser Xaa Leu Gly
1 5 10 15
Leu Val Thr Phe Leu Leu Asn His Ser Ala Ala Gly Gly Ser Pro Gln
20 25 30
His Arg Trp Leu Leu Leu Xaa
35

<210> 333
<211> 72
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (58)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (72)

213

<223> Xaa equals stop translation

<400> 333

Met Lys Ala Ile Ala Arg Ala Cys Leu Leu Leu Ser Leu Leu Val Leu
 1 5 10 15

Pro His Val Val Ser Glu His Leu Phe Trp His His Asn Pro Arg His
 20 25 30

Pro Val Ile Trp Pro Phe Pro Pro Phe His Leu Ile Ser Cys Ser Val
 35 40 45

Ser Ala Ser Thr Trp His Leu Gly Glu Xaa Leu Leu Leu Leu Val Pro
 50 55 60

Ile Ala Pro Ser Val Trp Ser Xaa
 65 70

<210> 334

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (62)

<223> Xaa equals stop translation

<400> 334

Met Glu Gln Gly Gly Gly Pro Arg Leu Leu Leu Leu Ile Pro Gly Leu
 1 5 10 15

Leu His Asn Thr Tyr Leu Ala Arg Pro Gly Asp Phe Pro Ala Gln Gly
 20 25 30

Thr Thr Glu Asn Thr Glu Cys Gln Gly Ser Pro Ser Pro Ile Ser His
 35 40 45

Leu Gly Lys Val Arg Ser Leu Asp Ser Asn Thr Gln Ile Xaa
 50 55 60

<210> 335

<211> 286

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (286)

<223> Xaa equals stop translation

<400> 335

Met Pro Leu Leu Phe Phe Ser Val Ser Thr Leu Phe Ser Gly Ser Val
 1 5 10 15

Thr Leu Gln Gln Arg Gly Met Phe Leu Pro Trp Thr Gly Thr Gly Glu

214

20					25					30						
Gln	Val	Leu	Ala	Leu	Leu	Trp	Pro	Arg	Phe	Glu	Leu	Ile	Leu	Glu	Met	
35					40					45						
Asn	Val	Gln	Ser	Val	Arg	Ser	Thr	Asp	Pro	Gln	Arg	Leu	Gly	Gly	Leu	
50					55					60						
Asp	Thr	Arg	Pro	His	Tyr	Ile	Thr	Arg	Arg	Tyr	Ala	Glu	Phe	Ser	Ser	
65					70					75					80	
Ala	Leu	Val	Ser	Ile	Asn	Gln	Thr	Ile	Pro	Asn	Glu	Arg	Thr	Met	Gln	
85					90					95						
Leu	Leu	Gly	Gln	Leu	Gln	Val	Glu	Val	Glu	Asn	Phe	Val	Leu	Arg	Val	
100					105					110						
Ala	Ala	Glu	Phe	Ser	Ser	Arg	Lys	Glu	Gln	Leu	Val	Phe	Leu	Ile	Asn	
115					120					125						
Asn	Tyr	Asp	Met	Met	Leu	Gly	Val	Leu	Met	Glu	Arg	Ala	Ala	Asp	Asp	
130					135					140						
Ser	Lys	Glu	Val	Glu	Ser	Phe	Gln	Gln	Leu	Leu	Asn	Ala	Arg	Thr	Gln	
145					150					155					160	
Glu	Phe	Ile	Glu	Glu	Leu	Leu	Ser	Pro	Pro	Phe	Gly	Gly	Leu	Val	Ala	
165					170					175						
Phe	Val	Lys	Glu	Ala	Glu	Ala	Leu	Ile	Glu	Arg	Gly	Gln	Ala	Glu	Arg	
180					185					190						
Leu	Arg	Gly	Glu	Glu	Ala	Arg	Val	Thr	Gln	Leu	Ile	Arg	Gly	Phe	Gly	
195					200					205						
Ser	Ser	Trp	Lys	Ser	Ser	Val	Glu	Ser	Leu	Ser	Gln	Asp	Val	Met	Arg	
210					215					220						
Ser	Phe	Thr	Asn	Phe	Arg	Asn	Gly	Thr	Ser	Ile	Ile	Gln	Gly	Ala	Leu	
225					230					235					240	
Thr	Gln	Leu	Ile	Gln	Leu	Tyr	His	Arg	Phe	His	Arg	Val	Leu	Ser	Gln	
245					250					255						
Pro	Gln	Leu	Arg	Ala	Leu	Pro	Ala	Arg	Ala	Glu	Leu	Ile	Asn	Ile	His	
260					265					270						
His	Leu	Met	Val	Glu	Leu	Lys	Lys	His	Lys	Pro	Asn	Phe	Xaa			
275					280					285						

<210> 336

<211> 55

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

215

<222> (55)

<223> Xaa equals stop translation

<400> 336

Met Phe Arg Ala Leu Arg Asp Leu Leu Thr His Tyr Pro Gln Gln Ile
 1 5 10 15

Leu Leu Gln Val Leu Val Val Met Tyr Gln Val Leu Gln Val Trp Glu
 20 25 30

Leu Pro Trp Pro Glu Leu Ile His Leu Gln Gly Ile Val Pro Thr Asp
 35 40 45

Gln Leu His Leu Lys Gln Xaa
 50 55

<210> 337

<211> 59

<212> PRT

<213> Homo sapiens

<400> 337

Met Ser Tyr Pro Leu Phe Leu Phe Met Ser Cys Met Val Ile Ser Leu
 1 5 10 15

Ser Pro Asn Ala Gly Ser Gln Thr Ser Thr Val Arg Cys Leu Ser Asp
 20 25 30

Leu Val Thr Phe Thr Leu Ile Lys Gly Ser Pro Val His Gln Thr Pro
 35 40 45

Tyr Leu Glu Ser Ser Ile Asn Cys Ile Thr Phe
 50 55

<210> 338

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (120)

<223> Xaa equals stop translation

<400> 338

Met His Pro Ala Arg Lys Leu Leu Ser Leu Leu Phe Leu Ile Leu Met
 1 5 10 15

Gly Thr Glu Leu Thr Gln Asp Ser Ala Ala Pro Asp Ser Leu Leu Arg
 20 25 30

Ser Ser Lys Gly Ser Thr Arg Gly Ser Leu Ala Ala Ile Val Ile Trp
 35 40 45

Arg Gly Lys Ser Glu Ser Arg Ile Ala Lys Thr Pro Gly Ile Phe Arg
 50 55 60

216

Gly Gly Gly Thr Leu Val Leu Pro Pro Thr His Thr Pro Glu Trp Leu
65 70 75 80

Ile Leu Pro Leu Gly Ile Thr Leu Pro Leu Gly Ala Pro Glu Thr Gly
85 90 95

Gly Gly Asp Cys Ala Ala Glu Thr Trp Lys Gly Ser Gln Arg Ala Gly
100 105 110

Gln Leu Cys Ala Leu Leu Ala Xaa
115 120

<210> 339

<211> 38

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 339

Met Pro Ser Phe Phe Leu Ser Leu Ile Gln Thr Asn Thr Leu Gly Ser
1 5 10 15

Ala Ser Phe Leu Leu Phe Leu Thr Leu His Ile His Leu Ser Pro Asn
20 25 30

Xaa Val His Ser Ala Ser
35

<210> 340

<211> 46

<212> PRT

<213> Homo sapiens

<400> 340

Met Phe Ser Arg Thr Ser Asn Phe Trp Thr Phe Phe Phe Gln Phe Leu
1 5 10 15

Ile Phe Lys Val Phe Leu Val Leu Lys Asn Leu Phe Thr Ser Gln Lys
20 25 30

Ile Tyr Lys Ile Tyr Ser Glu Lys Pro Lys Lys Lys Lys Lys
35 40 45

<210> 341

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

217

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (62)

<223> Xaa equals stop translation

<400> 341

Met	Ser	Ser	Leu	Leu	Ser	Ala	Gly	Leu	Gln	Ala	Ser	Leu	Cys	Gly	Lys
1				5				10					15		

Xaa	Leu	Trp	Ala	Ser	Thr	Trp	Tyr	Leu	Val	Cys	Cys	Leu	Leu	Pro	Phe
		20					25						30		

Phe	His	Gln	Gly	Cys	Cys	Asp	His	Lys	Ser	Lys	Gln	Gln	Tyr	Ile	Pro
	35						40					45			

Asn	Leu	Lys	Ser	Tyr	Cys	Gly	Leu	Ser	Thr	Ile	Glu	Ile	Xaa
	50				55						60		

<210> 342

<211> 87

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (87)

<223> Xaa equals stop translation

<400> 342

Met	Val	Leu	Phe	Cys	Phe	Val	Leu	Phe	Cys	Phe	Val	Phe	Glu	Met	Asp
1				5				10					15		

Ser	Ser	Ser	Val	Thr	Gln	Ala	Gly	Val	Gln	Trp	Cys	Asp	Leu	Gly	Ser
			20				25						30		

Leu	Gln	Ala	Pro	Pro	Pro	Gly	Phe	Ser	Pro	Phe	Ser	Cys	Leu	Ser	Leu
	35					40						45			

Pro	Ser	Ser	Trp	Asp	Tyr	Arg	Arg	Pro	Pro	Pro	Arg	Pro	Ala	Asn	Phe
	50					55					60				

Leu	Tyr	Phe	Leu	Val	Glu	Thr	Gly	Phe	His	His	Val	Ser	Gln	Asp	Gly
	65				70				75					80	

Leu	Asp	Leu	Leu	Thr	Ser	Xaa
				85		

<210> 343

<211> 538

<212> PRT

<213> Homo sapiens

<220>

218

<221> SITE

<222> (538)

<223> Xaa equals stop translation

<400> 343

Met	Ser	Thr	Lys	Lys	Leu	Cys	Ile	Val	Gly	Gly	Ile	Leu	Leu	Val	Phe
1				5					10					15	

Gln	Ile	Ile	Ala	Phe	Leu	Val	Gly	Gly	Leu	Ile	Ala	Pro	Gly	Pro	Thr
			20					25					30		

Thr	Ala	Val	Ser	Tyr	Met	Ser	Val	Lys	Cys	Val	Asp	Ala	Arg	Lys	Asn
		35						40				45			

His	His	Lys	Thr	Lys	Trp	Phe	Val	Pro	Trp	Gly	Pro	Asn	His	Cys	Asp
	50					55					60				

Lys	Ile	Arg	Asp	Ile	Glu	Glu	Ala	Ile	Pro	Arg	Glu	Ile	Glu	Ala	Asn
65					70					75					80

Asp	Ile	Val	Phe	Ser	Val	His	Ile	Pro	Leu	Pro	His	Met	Glu	Met	Ser
				85					90					95	

Pro	Trp	Phe	Gln	Phe	Met	Leu	Phe	Ile	Leu	Gln	Leu	Asp	Ile	Ala	Phe
			100					105					110		

Lys	Leu	Asn	Asn	Gln	Ile	Arg	Glu	Asn	Ala	Glu	Val	Ser	Met	Asp	Val
	115						120					125			

Ser	Leu	Ala	Tyr	Arg	Asp	Asp	Ala	Phe	Ala	Glu	Trp	Thr	Glu	Met	Ala
	130					135					140				

His	Glu	Arg	Val	Pro	Arg	Lys	Leu	Lys	Cys	Thr	Phe	Thr	Ser	Pro	Lys
145						150				155					160

Thr	Pro	Glu	His	Glu	Gly	Arg	Tyr	Tyr	Glu	Cys	Asp	Val	Leu	Pro	Phe
				165					170					175	

Met	Glu	Ile	Gly	Ser	Val	Ala	His	Lys	Phe	Tyr	Leu	Leu	Asn	Ile	Arg
		180						185					190		

Leu	Pro	Val	Asn	Glu	Lys	Lys	Lys	Ile	Asn	Val	Gly	Ile	Gly	Glu	Ile
		195					200					205			

Lys	Asp	Ile	Arg	Leu	Val	Gly	Ile	His	Gln	Asn	Gly	Gly	Phe	Thr	Lys
	210					215					220				

Val	Trp	Phe	Ala	Met	Lys	Thr	Phe	Leu	Thr	Pro	Ser	Ile	Phe	Ile	Ile
225					230					235					240

Met	Val	Trp	Tyr	Trp	Arg	Arg	Ile	Thr	Met	Met	Ser	Arg	Pro	Pro	Val
				245					250					255	

Leu	Leu	Glu	Lys	Val	Ile	Phe	Ala	Leu	Gly	Ile	Ser	Met	Thr	Phe	Ile
			260					265					270		

Asn	Ile	Pro	Val	Glu	Trp	Phe	Ser	Ile	Gly	Phe	Asp	Trp	Thr	Trp	Met
		275						280					285		

219

Leu Leu Phe Gly Asp Ile Arg Gln Gly Ile Phe Tyr Ala Met Leu Leu
 290 295 300
 Ser Phe Trp Ile Ile Phe Cys Gly Glu His Met Met Asp Gln His Glu
 305 310 315 320
 Arg Asn His Ile Ala Gly Tyr Trp Lys Gln Val Gly Pro Ile Ala Val
 325 330 335
 Gly Ser Phe Cys Leu Phe Ile Phe Asp Met Cys Glu Arg Gly Val Gln
 340 345 350
 Leu Thr Asn Pro Phe Tyr Ser Ile Trp Thr Thr Asp Ile Gly Thr Glu
 355 360 365
 Leu Ala Met Ala Phe Ile Ile Val Ala Gly Ile Cys Leu Cys Leu Tyr
 370 375 380
 Phe Leu Phe Leu Cys Phe Met Val Phe Gln Val Phe Arg Asn Ile Ser
 385 390 395 400
 Gly Lys Gln Ser Ser Leu Pro Ala Met Ser Lys Val Arg Arg Leu His
 405 410 415
 Tyr Glu Gly Leu Ile Phe Arg Phe Lys Phe Leu Met Leu Ile Thr Leu
 420 425 430
 Ala Cys Ala Ala Met Thr Val Ile Phe Phe Ile Val Ser Gln Val Thr
 435 440 445
 Glu Gly His Trp Lys Trp Gly Gly Val Thr Val Gln Val Asn Ser Ala
 450 455 460
 Phe Phe Thr Gly Ile Tyr Gly Met Trp Asn Leu Tyr Val Phe Ala Leu
 465 470 475 480
 Met Phe Leu Tyr Ala Pro Ser His Lys Asn Tyr Gly Glu Asp Gln Ser
 485 490 495
 Asn Gly Met Gln Leu Pro Cys Lys Ser Arg Glu Asp Cys Ala Leu Phe
 500 505 510
 Val Ser Glu Leu Tyr Gln Glu Leu Phe Ser Ala Ser Lys Tyr Ser Phe
 515 520 525
 Ile Asn Asp Asn Ala Ala Ser Gly Ile Xaa
 530 535

<210> 344

<211> 202

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (202)

220

<223> Xaa equals stop translation

<400> 344

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Met Gly Ile Ala Leu Ala Val Leu Gly Trp Leu Ala Val Met Leu Cys
 1             5             10             15

Cys Ala Leu Pro Met Trp Arg Val Thr Ala Phe Ile Gly Ser Asn Ile
      20             25             30

Val Thr Ser Gln Thr Ile Trp Glu Gly Leu Trp Met Asn Cys Val Val
      35             40             45

Gln Ser Thr Gly Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala
      50             55             60

Leu Pro Gln Asp Leu Gln Ala Ala Arg Ala Leu Val Ile Ile Ser Ile
      65             70             75             80

Ile Val Ala Ala Leu Gly Val Leu Leu Ser Val Val Gly Gly Lys Cys
      85             90             95

Thr Asn Cys Leu Glu Asp Glu Ser Ala Lys Ala Lys Thr Met Ile Val
      100             105             110

Ala Gly Val Val Phe Leu Leu Ala Gly Leu Met Val Ile Val Pro Val
      115             120             125

Ser Trp Thr Ala His Asn Ile Ile Gln Asp Phe Tyr Asn Pro Leu Val
      130             135             140

Ala Ser Gly Gln Lys Arg Glu Met Gly Ala Ser Leu Tyr Val Gly Trp
      145             150             155             160

Ala Ala Ser Gly Leu Leu Leu Leu Gly Gly Gly Leu Leu Cys Cys Asn
      165             170             175

Cys Pro Pro Arg Thr Asp Lys Pro Tyr Ser Ala Lys Tyr Ser Ala Ala
      180             185             190

Arg Ser Ala Ala Ala Ser Asn Tyr Val Xaa
      195             200

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<210> 345

<211> 122

<212> PRT

<213> Homo sapiens

<400> 345

```

Met Val Ser Ile Ser Val Val Leu Arg Val Ser Leu Pro Thr Leu Glu
 1             5             10             15

Pro Val Pro Val Ala Gly Arg Ser Ile Trp Ile Ser Thr Thr Ser Pro
      20             25             30

Ser Met Ile Ser Val Ser Ser Leu Met Arg Thr Pro Met Asp Arg Arg
      35             40             45

```


221

Lys Ala Cys Val Ser Ala Ser Val Leu Leu Ile Ser Arg Glu Lys Ile
 50 55 60

Ser Leu Pro Ala Met Ala Val Asn Gly Val Ser Gly Pro Arg Ala Cys
 65 70 75 80

Ala Met Pro Met Ala Met Ala Val Phe Pro Val Pro Gly Trp Pro Ala
 85 90 95

Ile Arg Thr Ala Arg Pro Ala Ile Phe Pro Ser Arg Ile Ile Ser Ser
 100 105 110

Thr Thr Pro Ala Ala Arg Arg Ala Ala Ser
 115 120

<210> 346

<211> 260

<212> PRT

<213> Homo sapiens

<400> 346

Met Leu Ala Leu Leu Gly Leu Ser Gln Ala Leu Asn Ile Leu Leu Gly
 1 5 10 15

Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys Glu Lys Gly
 20 25 30

Asn Phe Asn Val Ala His Gly Leu Ala Trp Ser Tyr Tyr Ile Gly Tyr
 35 40 45

Leu Arg Leu Ile Leu Pro Glu Leu Gln Ala Arg Ile Arg Thr Tyr Asn
 50 55 60

Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln Arg Leu Tyr
 65 70 75 80

Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met Ala
 85 90 95

Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly Asp
 100 105 110

Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn Ser Ile Tyr Glu Leu
 115 120 125

Leu Glu Asn Gly Gln Arg Ala Gly Thr Cys Val Leu Glu Tyr Ala Thr
 130 135 140

Pro Leu Gln Thr Leu Phe Ala Met Ser Gln Tyr Ser Gln Ala Gly Phe
 145 150 155 160

Ser Gly Glu Asp Arg Leu Glu Gln Ala Lys Leu Phe Cys Arg Thr Leu
 165 170 175

Glu Asp Ile Leu Ala Asp Ala Pro Glu Ser Gln Asn Asn Cys Arg Leu
 180 185 190

222

Ile Ala Tyr Gln Glu Pro Ala Asp Asp Ser Ser Phe Ser Leu Ser Gln
 195 200 205

Glu Val Leu Arg His Leu Arg Gln Glu Glu Lys Glu Glu Val Thr Val
 210 215 220

Gly Ser Leu Lys Thr Ser Ala Val Pro Ser Thr Ser Thr Met Ser Gln
 225 230 235 240.

Glu Pro Glu Leu Leu Ile Ser Gly Met Glu Lys Pro Leu Pro Leu Arg
 245 250 255

Thr Asp Phe Ser
 260

<210> 347
 <211> 48
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (48)
 <223> Xaa equals stop translation

<400> 347
 Met Thr Pro Gln Lys Pro Ala Leu Ala Val Leu Leu Leu Glu Val Pro
 1 5 10 15

Leu Leu Leu Thr Leu Ser Val Leu Lys Lys Arg Cys Leu Val Thr Cys
 20 25 30

Glu Pro Thr Ser Arg Phe Val Ser Cys Asp Leu Pro Leu Ser Val Xaa
 35 40 45

<210> 348
 <211> 334
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (288)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (334)
 <223> Xaa equals stop translation

<400> 348
 Met Ala Ala Ala Ala Trp Leu Gln Val Leu Pro Val Ile Leu Leu Leu
 1 5 10 15

223

Leu Gly Ala His Pro Ser Pro Leu Ser Phe Phe Ser Ala Gly Pro Ala
 20 25 30
 Thr Val Ala Ala Ala Asp Arg Ser Lys Trp His Ile Pro Ile Pro Ser
 35 40 45
 Gly Lys Asn Tyr Phe Ser Phe Gly Lys Ile Leu Phe Arg Asn Thr Thr
 50 55 60
 Ile Phe Leu Lys Phe Asp Gly Glu Pro Cys Asp Leu Ser Leu Asn Ile
 65 70 75 80
 Thr Trp Tyr Leu Lys Ser Ala Asp Cys Tyr Asn Glu Ile Tyr Asn Phe
 85 90 95
 Lys Ala Glu Glu Val Glu Leu Tyr Leu Glu Lys Leu Lys Glu Lys Arg
 100 105 110
 Gly Leu Ser Gly Lys Tyr Gln Thr Ser Ser Lys Leu Phe Gln Asn Cys
 115 120 125
 Ser Glu Leu Phe Lys Thr Gln Thr Phe Ser Gly Asp Phe Met His Arg
 130 135 140
 Leu Pro Leu Leu Gly Glu Lys Gln Glu Ala Lys Glu Asn Gly Thr Asn
 145 150 155 160
 Leu Thr Phe Ile Gly Asp Lys Thr Ala Met His Glu Pro Leu Gln Thr
 165 170 175
 Trp Gln Asp Ala Pro Tyr Ile Phe Ile Val His Ile Gly Ile Ser Ser
 180 185 190
 Ser Lys Glu Ser Ser Lys Glu Asn Ser Leu Ser Asn Leu Phe Thr Met
 195 200 205
 Thr Val Glu Val Lys Gly Pro Tyr Glu Tyr Leu Thr Leu Glu Asp Tyr
 210 215 220
 Pro Leu Met Ile Phe Phe Met Val Met Cys Ile Val Tyr Val Leu Phe
 225 230 235 240
 Gly Val Leu Trp Leu Ala Trp Ser Ala Cys Tyr Trp Arg Asp Leu Leu
 245 250 255
 Arg Ile Gln Phe Trp Ile Gly Ala Val Ile Phe Leu Gly Met Leu Glu
 260 265 270
 Lys Ala Val Phe Tyr Ala Glu Phe Gln Asn Ile Arg Tyr Lys Gly Xaa
 275 280 285
 Ser Val Gln Gly Ala Leu Ile Leu Ala Glu Leu Leu Ser Ala Val Lys
 290 295 300
 Arg Ser Leu Ala Arg Thr Leu Val Ile Ile Val Ser Leu Gly Tyr Gly
 305 310 315 320

224

Ile Val Lys Pro Arg Leu Glu Ser Leu Phe Ile Arg Leu Xaa
 325 330

<210> 349

<211> 200

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (193)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (200)

<223> Xaa equals stop translation

<400> 349

Met Val Leu Xaa Val Val Thr Leu Gly Leu Ala Leu Phe Thr Leu Cys
 1 5 10 15

Gly Lys Phe Lys Arg Trp Lys Leu Asn Gly Ala Phe Leu Leu Ile Thr
 20 25 30

Ala Phe Leu Ser Val Leu Ile Trp Val Ala Trp Met Thr Met Tyr Leu
 35 40 45

Phe Gly Asn Val Lys Leu Gln Gln Gly Asp Ala Trp Asn Asp Pro Thr
 50 55 60

Leu Ala Ile Thr Leu Ala Ala Ser Ala Gly Ser Ser Ser Ser Ser Thr
 65 70 75 80

Pro Ser Leu Arg Ser Thr Ala Pro Phe Cys Gln Pro Cys Arg Arg Thr
 85 90 95

Arg Pro Thr Thr Ser Thr Arg Arg Ser Pro Gly Cys Gly Arg Arg Pro
 100 105 110

Ser Arg Arg Thr Cys Ser Cys Arg Gly Pro Ile Trp Arg Thr Arg Pro
 115 120 125

Ser Pro Trp Met Asn Thr Met Gln Leu Ser Glu Gln Gln Asp Phe Pro
 130 135 140

Thr Ala Ala Trp Glu Lys Asp Pro Val Ala Ala Trp Gly Lys Asp Pro
 145 150 155 160

Ala Leu Arg Leu Glu Ala Thr Cys Ile Ser Gln Leu Arg Trp Pro Ser
 165 170 175

225

Cys Ser Thr Val Gly Pro Ser Gln Leu Leu Arg Gln Val Thr Gln Glu
180 185 190

Xaa Thr Phe Gly Glu Arg Leu Xaa
195 200

<210> 350
<211> 24
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (24)
<223> Xaa equals stop translation

<400> 350
Met Leu Leu His His Gln Leu Leu Ile Val Thr Leu His Leu Val Leu
1 5 10 15

Leu Leu Ala Thr Leu Leu Val Xaa
20

<210> 351
<211> 143
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (85)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (131)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (143)
<223> Xaa equals stop translation

<400> 351
Met Thr Lys Ala Leu Leu Ile Tyr Leu Val Ser Ser Phe Leu Ala Leu
1 5 10 15

Asn Gln Ala Ser Leu Ile Ser Arg Cys Asp Leu Ala Gln Val Leu Gln
20 25 30

Leu Glu Asp Leu Asp Gly Phe Glu Gly Tyr Ser Leu Ser Asp Trp Leu
35 40 45

Cys Leu Ala Phe Val Glu Ser Lys Phe Asn Ile Ser Lys Ile Asn Glu
50 55 60

226

Asn Ala Asp Gly Ser Phe Asp Tyr Gly Leu Phe Gln Ile Asn Ser His
 65 70 75 80

Tyr Trp Cys Asn Xaa Tyr Lys Ser Tyr Ser Glu Asn Leu Cys His Val
 85 90 95

Asp Cys Gln Asp Leu Leu Asn Pro Asn Leu Leu Ala Gly Ile His Cys
 100 105 110

Ala Lys Arg Ile Val Ser Gly Ala Arg Gly Met Asn Asn Trp Val Arg
 115 120 125

Met Glu Xaa Cys Thr Val Gln Ala Gly His Ser Ser Thr Gly Xaa
 130 135 140

<210> 352
 <211> 95
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (95)
 <223> Xaa equals stop translation

<400> 352
 Met Leu Val Ile Ala Gly Gly Ile Leu Ala Ala Leu Leu Leu Ile
 1 5 10 15

Val Val Val Leu Cys Leu Tyr Phe Lys Ile His Asn Ala Leu Lys Ala
 20 25 30

Ala Lys Glu Pro Glu Ala Val Ala Val Lys Asn His Asn Pro Asp Lys
 35 40 45

Val Trp Trp Ala Lys Asn Ser Gln Ala Lys Thr Ile Ala Thr Glu Ser
 50 55 60

Cys Pro Ala Leu Gln Cys Cys Glu Gly Tyr Arg Met Cys Ala Ser Phe
 65 70 75 80

Asp Ser Leu Pro Pro Cys Cys Cys Asp Ile Asn Glu Gly Leu Xaa
 85 90 95

<210> 353
 <211> 38
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (38)
 <223> Xaa equals stop translation

<400> 353
 Met Leu Leu Lys Ser Asn Ile Leu Met Leu Asn Leu Phe Ala Ala Asn

227

1 5 10 15
 Val Gly Ala Asn Phe Ala Leu Thr Val Glu Lys Ile Gly Met Ile Leu
 20 25 30

Leu Asn Val Ser Gly Xaa
 35

<210> 354
 <211> 39
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (39)
 <223> Xaa equals stop translation

<400> 354
 Met Leu Val Val Ala Phe Gly Leu Leu Val Leu Tyr Ile Leu Leu Ala
 1 5 10 15

Ser Ser Trp Lys Arg Pro Glu Pro Gly Ile Leu Thr Asp Arg Gln Pro
 20 25 30

Leu Leu His Asp Gly Glu Xaa
 35

<210> 355
 <211> 71
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (71)
 <223> Xaa equals stop translation

<400> 355
 Ser Asp Pro Leu Ala Ser Ala Ser Gln Asn Ala Gly Ile Val Ser Val
 1 5 10 15

Gly Leu Cys Thr Arg Pro Gly Pro Gln Phe Lys Asn Ala Gln Pro Pro
 20 25 30

Phe Pro Xaa Gln Lys Ala Pro Arg Cys Leu Trp Glu Asn Gln Pro Pro
 35 40 45

Pro Trp Arg Lys Ala Trp Asp Leu Pro Ser His Leu Gly Arg Arg Gly
 50 55 60

228

Ile Cys Gly Lys Ser Phe Xaa
65 70

<210> 356

<211> 227

<212> PRT

<213> Homo sapiens

<400> 356

Met Ala Asp Leu Leu Gly Ser Ile Leu Ser Ser Met Glu Lys Pro Pro
1 5 10 15

Ser Leu Gly Asp Gln Glu Thr Arg Arg Lys Ala Arg Glu Gln Ala Ala
20 25 30

Arg Leu Lys Lys Leu Gln Glu Gln Glu Lys Gln Gln Lys Val Glu Phe
35 40 45

Arg Lys Arg Met Glu Lys Glu Val Ser Asp Phe Ile Gln Asp Ser Gly
50 55 60

Gln Ile Lys Lys Lys Phe Gln Pro Met Asn Lys Ile Glu Arg Ser Ile
65 70 75 80

Leu His Asp Val Val Glu Val Ala Gly Leu Thr Ser Phe Ser Phe Gly
85 90 95

Glu Asp Asp Asp Cys Arg Tyr Val Met Ile Phe Lys Lys Glu Phe Ala
100 105 110

Pro Ser Asp Glu Glu Leu Asp Ser Tyr Arg Arg Gly Glu Glu Trp Asp
115 120 125

Pro Gln Lys Ala Glu Glu Lys Arg Lys Leu Lys Glu Leu Ala Gln Arg
130 135 140

Gln Glu Glu Glu Ala Ala Gln Gln Gly Pro Val Val Val Ser Pro Ala
145 150 155 160

Ser Asp Tyr Lys Asp Lys Tyr Ser His Leu Ile Gly Lys Gly Ala Ala
165 170 175

Lys Asp Ala Ala His Met Leu Gln Ala Asn Lys Thr Tyr Gly Cys Val
180 185 190

Pro Val Ala Asn Lys Arg Asp Thr Arg Ser Ile Glu Glu Ala Met Asn
195 200 205

Glu Ile Arg Ala Lys Lys Arg Leu Arg Gln Ser Gly Glu Glu Leu Pro
210 215 220

Pro Thr Ser
225

<210> 357

<211> 90

229

<212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (50)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (53)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (59)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (60)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (61)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (64)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (65)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (90)
 <223> Xaa equals stop translation

<400> 357

Met Trp Asp Trp Asp Trp Ser Ala Pro Trp Ser Trp Pro Leu Trp Leu
 1 5 10 15

Ser Leu Ala Leu Val Cys Leu Ser Ala Gly Ala Lys Gly His Arg Ala
 20 25 30

Ser Glu Ala Gly His Ala Arg Ala Leu Thr Cys Glu Met Gly Ser Glu
 35 40 45

Phe Xaa Thr Ala Xaa Gly Leu Val Leu Gly Xaa Xaa Xaa Trp Thr Xaa
 50 55 60

Xaa Asn Gly Ser Ala Gly Pro Glu Arg Arg Gly Trp Arg Pro Ala Ala
 65 70 75 80

230

Phe Leu Ala Val Phe Leu Leu Gly Asp Xaa
 85 90

<210> 358

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 358

Met Phe Gly Pro Thr Phe His Ser Leu Val Leu Val Pro Pro Trp Pro
 1 5 10 15

Asn Leu Ser Leu Leu His Phe Thr Ser Pro Val Gly Gln His Ser Ser
 20 25 30

Phe Leu Pro Thr Ser Leu Arg Leu Xaa Lys Lys Lys Lys Lys Lys Lys
 35 40 45

<210> 359

<211> 56

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals stop translation

<400> 359

Met Cys Ser Lys Asn Gly Phe Leu Leu Ala Trp Ser Trp Asn Ser Pro
 1 5 10 15

Trp Leu Pro Gln Ala Ser Leu Ala His Gly Cys Trp Gly Arg Trp Met
 20 25 30

Ser Asp Leu Val Gly Cys Ser Arg Glu Asn Lys Cys Ala Leu Arg Asp
 35 40 45

His Ser Glu Arg Val Gln Gly Xaa
 50 55

<210> 360

<211> 222

<212> PRT

<213> Homo sapiens

231

<220>
 <221> SITE
 <222> (4)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (222)
 <223> Xaa equals stop translation

 <400> 360
 Ser Pro Leu Xaa Phe Cys Val Val Leu Leu Leu Gln Ala Ala Arg Gly
 1 5 10 15
 Tyr Val Val Arg Lys Pro Ala Gln Ser Arg Leu Asp Asp Asp Pro Pro
 20 25 30
 Pro Ser Thr Leu Leu Lys Asp Tyr Gln Asn Val Pro Gly Ile Glu Lys
 35 40 45
 Val Asp Asp Val Val Lys Arg Leu Leu Ser Leu Glu Met Ala Asn Lys
 50 55 60
 Lys Glu Met Leu Lys Ile Lys Gln Glu Gln Phe Met Lys Lys Ile Val
 65 70 75 80
 Ala Asn Pro Glu Asp Thr Arg Ser Leu Glu Ala Arg Ile Ile Ala Leu
 85 90 95
 Ser Val Lys Ile Arg Ser Tyr Glu Glu His Leu Glu Lys His Arg Lys
 100 105 110
 Asp Lys Ala His Lys Arg Tyr Leu Leu Met Ser Ile Asp Gln Arg Lys
 115 120 125
 Lys Met Leu Lys Asn Leu Arg Asn Thr Asn Tyr Asp Val Phe Glu Lys
 130 135 140
 Ile Cys Trp Gly Leu Gly Ile Glu Tyr Thr Phe Pro Pro Leu Tyr Tyr
 145 150 155 160
 Arg Arg Ala His Arg Arg Phe Val Thr Lys Lys Ala Leu Cys Ile Arg
 165 170 175
 Val Phe Gln Glu Thr Gln Lys Leu Lys Lys Arg Arg Arg Ala Leu Lys
 180 185 190
 Ala Ala Ala Ala Ala Gln Lys Gln Ala Lys Arg Arg Asn Pro Asp Ser
 195 200 205
 Pro Ala Lys Ala Ile Pro Lys Thr Leu Lys Asp Ser Gln Xaa
 210 215 220

<210> 361
 <211> 432

232

<212> PRT

<213> Homo sapiens

<400> 361

Met Gly Ala Pro Ala Ala Ser Leu Leu Leu Leu Leu Leu Phe Ala
 1 5 10 15
 Cys Cys Trp Ala Pro Gly Gly Ala Asn Leu Ser Gln Asp Gly Tyr Trp
 20 25 30
 Gln Glu Gln Asp Leu Glu Leu Gly Thr Leu Ala Pro Leu Asp Glu Ala
 35 40 45
 Ile Ser Ser Thr Val Trp Ser Ser Pro Asp Met Leu Ala Ser Gln Asp
 50 55 60
 Ser Gln Pro Trp Thr Ser Asp Glu Thr Val Val Ala Gly Gly Thr Val
 65 70 75 80
 Val Leu Lys Cys Gln Val Lys Asp His Glu Asp Ser Ser Leu Gln Trp
 85 90 95
 Ser Asn Pro Ala Gln Gln Thr Leu Tyr Phe Gly Glu Lys Arg Ala Leu
 100 105 110
 Arg Asp Asn Arg Ile Gln Leu Val Thr Ser Thr Pro His Glu Leu Ser
 115 120 125
 Ile Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu Tyr Thr Cys
 130 135 140
 Ser Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu Val Thr Val
 145 150 155 160
 Leu Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys Ser Ser Leu
 165 170 175
 Arg Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser Gly Ser Lys
 180 185 190
 Pro Ala Ala Arg Leu Thr Trp Arg Lys Gly Asp Gln Glu Leu His Gly
 195 200 205
 Glu Pro Thr Arg Ile Gln Glu Asp Pro Asn Gly Lys Thr Phe Thr Val
 210 215 220
 Ser Ser Ser Val Thr Phe Gln Val Thr Arg Glu Asp Asp Gly Ala Ser
 225 230 235 240
 Ile Val Cys Ser Val Asn His Glu Ser Leu Lys Gly Ala Asp Arg Ser
 245 250 255
 Thr Ser Gln Arg Ile Glu Val Leu Tyr Thr Pro Thr Ala Met Ile Arg
 260 265 270
 Pro Asp Pro Pro His Pro Arg Glu Gly Gln Lys Leu Leu Leu His Cys
 275 280 285

233

Glu Gly Arg Gly Asn Pro Val Pro Gln Gln Tyr Leu Trp Glu Lys Glu
 290 295 300
 Gly Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser Ala Leu Ile Phe
 305 310 315 320
 Pro Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly Cys Thr Ala Thr
 325 330 335
 Ser Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu Asn Val Asn Asp
 340 345 350
 Pro Ser Pro Val Pro Ser Ser Ser Ser Thr Tyr His Ala Ile Ile Gly
 355 360 365
 Gly Ile Val Ala Phe Ile Val Phe Leu Leu Leu Ile Met Leu Ile Phe
 370 375 380
 Leu Gly His Tyr Leu Ile Arg His Lys Gly Thr Tyr Leu Thr His Glu
 385 390 395 400
 Ala Lys Gly Ser Asp Asp Ala Pro Asp Ala Asp Thr Ala Ile Ile Asn
 405 410 415
 Ala Glu Gly Gly Gln Ser Gly Gly Asp Asp Lys Lys Glu Tyr Phe Ile
 420 425 430

<210> 362

<211> 154

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (125)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (144)

<223> Xaa equals any of the naturally occurring L-amino acids

234

<220>

<221> SITE

<222> (154)

<223> Xaa equals stop translation

<400> 362

Met Val Ala Pro Val Trp Tyr Leu Val Ala Ala Ala Leu Leu Val Gly
 1 5 10 15

Phe Ile Leu Phe Leu Thr Arg Ser Arg Gly Arg Ala Ala Ser Ala Gly
 20 25 30

Gln Glu Pro Leu His Asn Glu Glu Leu Ala Gly Ala Gly Arg Val Ala
 35 40 45

Gln Pro Gly Pro Leu Glu Pro Glu Glu Pro Arg Ala Gly Gly Arg Pro
 50 55 60

Arg Arg Arg Arg Asp Leu Gly Ser Arg Leu Gln Ala Gln Arg Arg Ala
 65 70 75 80

Gln Arg Val Ala Trp Ala Glu Ala Asp Glu Asn Glu Glu Glu Ala Val
 85 90 95

Ile Leu Ala Gln Glu Glu Glu Gly Val Glu Lys Pro Ala Glu Xaa His
 100 105 110

Leu Ser Gly Lys Ile Gly Ala Lys Lys Leu Arg Xaa Xaa Glu Glu Lys
 115 120 125

Gln Ala Arg Lys Ala Gln Xaa Glu Ala Glu Glu Ala Glu Arg Glu Xaa
 130 135 140

Arg Lys Arg Leu Glu Ser Gln Arg Glu Xaa
 145 150

<210> 363

<211> 17

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (17)

<223> Xaa equals stop translation

<400> 363

Met Gln Lys Cys Met Leu Ser Ala Leu Val Phe His Ile Gln Trp Ser
 1 5 10 15

Xaa

<210> 364

<211> 10

235

<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (10)
<223> Xaa equals stop translation

<400> 364
Met Leu Val Cys Ser Phe Leu Phe Leu Xaa
1 5 10

<210> 365
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (14)
<223> Xaa equals stop translation

<400> 365
Val Ile Glu Leu Cys Val Ser Leu Arg Ser Leu Asn Phe Xaa
1 5 10

<210> 366
<211> 18
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (10)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (18)
<223> Xaa equals stop translation

236

<400> 366

Met Cys Glu Phe Xaa Xaa Xaa Ile Met Xaa Leu Ala Gly Tyr Phe Ala
1 5 10 15

Cys Xaa

<210> 367

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (62)

<223> Xaa equals stop translation

<400> 367

Met Val Gly Gly Tyr Val Ser Ser Phe Ser Phe Pro Pro Val Ser Ser
1 5 10 15

Ser Leu Leu Leu Pro Ala Ser Phe Ala Phe Pro Phe Leu Pro Gly Thr
20 25 30

Pro Cys Pro Phe Leu Tyr Phe Leu Pro Ser Pro Phe Ser Pro Leu Pro
35 40 45

Leu Ser Leu Thr Arg Ser Asn Ser Phe Leu Leu Asn Gly Xaa
50 55 60

<210> 368

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals stop translation

<400> 368

Glu Lys Lys Ser Met Ser Val Ser Asp Ile Tyr Ala Leu Glu Ser Leu
1 5 10 15

Gly Arg Ser Leu Phe Thr Leu Asn Ser Met Cys Leu Pro Leu Ser Phe
20 25 30

Xaa

<210> 369

<211> 245

<212> PRT

<213> Homo sapiens

237

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 369

Met Gly Gly Ala Ser Arg Arg Val Glu Ser Gly Ala Trp Ala Tyr Leu
 1 5 10 15

Ser Pro Leu Val Leu Arg Lys Glu Leu Glu Ser Leu Val Glu Asn Glu
 20 25 30

Gly Ser Glu Val Leu Ala Leu Pro Glu Leu Pro Ser Ala His Pro Ile
 35 40 45

Ile Phe Trp Asn Leu Leu Trp Tyr Phe Gln Arg Leu Arg Leu Pro Ser
 50 55 60

Ile Leu Pro Gly Leu Val Leu Ala Ser Cys Asp Gly Pro Ser Xaa Ser
 65 70 75 80

Gln Ala Pro Ser Pro Trp Leu Thr Pro Asp Pro Ala Ser Val Gln Val
 85 90 95

Arg Leu Leu Trp Asp Val Leu Thr Pro Asp Pro Asn Ser Cys Pro Pro
 100 105 110

Leu Tyr Val Leu Trp Arg Val His Ser Gln Ile Pro Gln Arg Val Val
 115 120 125

Trp Pro Gly Pro Val Pro Ala Ser Leu Ser Leu Ala Leu Leu Glu Ser
 130 135 140

Val Leu Arg His Val Gly Leu Asn Glu Val His Lys Ala Val Gly Leu
 145 150 155 160

Leu Leu Glu Thr Leu Gly Pro Pro Pro Thr Gly Leu His Leu Gln Arg
 165 170 175

Gly Ile Tyr Arg Glu Ile Leu Phe Leu Thr Met Ala Ala Leu Gly Lys
 180 185 190

Asp His Val Asp Ile Val Ala Phe Asp Lys Lys Tyr Lys Ser Ala Phe
 195 200 205

Asn Lys Leu Ala Ser Ser Met Gly Lys Glu Glu Leu Arg His Arg Arg
 210 215 220

Ala Gln Met Pro Thr Pro Lys Ala Ile Asp Cys Arg Lys Cys Phe Gly
 225 230 235 240

Ala Pro Pro Glu Cys
 245

<210> 370

<211> 35

<212> PRT

238

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals stop translation

<400> 370

Met	Lys	Phe	Ser	Leu	Leu	Phe	Leu	Pro	Met	Leu	Leu	Ile	Leu	Lys	Pro
1				5				10						15	

Asp	Leu	Phe	His	Ile	Ser	Ile	Cys	Thr	Leu	Ala	Ala	Cys	Gly	Leu	Thr
			20					25					30		

Phe	Pro	Xaa
		35

<210> 371

<211> 22

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals stop translation

<400> 371

Met	Leu	Phe	Phe	Phe	Ile	Leu	His	Leu	Leu	Ser	Ile	Met	Ser	Phe	Leu
1					5					10				15	

Ser	Pro	Asp	Ile	Met	Xaa
			20		

<210> 372

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (82)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 372

Met	Phe	Gly	Leu	Leu	Val	Glu	Ser	Gln	Thr	Leu	Leu	Glu	Glu	Asn	Ala
1					5					10				15	

Val	Gln	Gly	Thr	Glu	Arg	Thr	Leu	Gly	Leu	Asn	Ile	Ala	Pro	Phe	Ile
			20						25					30	

Asn	Gln	Phe	Gln	Val	Pro	Ile	Arg	Val	Phe	Leu	Asp	Leu	Ser	Ser	Leu
			35					40				45			

Pro	Cys	Ile	Pro	Leu	Ser	Lys	Pro	Val	Glu	Leu	Leu	Arg	Leu	Asp	Leu
						55						60			

239

Met Thr Pro Tyr Leu Asn Thr Ser Asn Arg Glu Val Lys Val Tyr Val
 65 70 75 80

Cys Xaa Ile Trp Glu Asp Leu Thr Ala Ile Pro Phe Trp Val Ser Tyr
 85 90 95

Val Pro

<210> 373
 <211> 78
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (42)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (43)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 373
 Met Phe Gly Ala His Arg Xaa Trp Gln Gly Ser Val Leu Leu Phe Leu
 1 5 10 15

Ser Phe Ala Trp Gly Asn Gly Gly Ser Val Thr Phe Ser Asp Val Pro
 20 25 30

Arg Val Met Pro Leu Ala Gly Gly Pro Xaa Xaa Gln Val Ser Ser Thr
 35 40 45

Pro Arg Pro Pro Pro His Gln Val Thr Ser Ser Pro Gly Leu Glu Ser
 50 55 60

Ala His Ile Val Cys Pro Glu Arg Lys Lys Lys Lys Lys Lys
 65 70 75

<210> 374
 <211> 31
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (4)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (20)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (25)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (28)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals stop translation

<400> 374
 Thr Leu Leu Xaa Phe Leu Xaa Leu Leu Thr Thr Glu Gly Gly Arg Glu
 1 5 10 15
 Asn Ile Phe Xaa Gly Arg Ile Leu Xaa Leu Gln Xaa Ser Pro Xaa
 20 25 30

<210> 375
 <211> 57
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (32)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (57)
 <223> Xaa equals stop translation

<400> 375
 Met Leu Ser Phe Phe Ile Cys Leu Leu Ile Phe Val His Leu Leu Leu
 1 5 10 15
 Leu Ser Phe Leu Ile Ser Asp Trp Pro Pro Pro Thr Gly Ser Ala Xaa
 20 25 30
 His Lys Ile Leu Arg Leu Met Val Val Gln Arg Leu Ser Leu Leu Asp
 35 40 45

241

Gln Arg Lys Arg Trp Ser Glu Ala Xaa
 50 55

<210> 376

<211> 63

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 376

Met Cys His His Ala Trp Leu Ile Phe Lys Phe Phe Val Xaa Met Gly
 1 5 10 15

Ser His Tyr Val Ala Gln Ala Gly Phe Arg Phe Leu Cys Ser Arg Asp
 20 25 30

Ser Ala Asn Leu Ala Pro Gln Ser Ala Gly Ile Thr Asn Val Ser His
 35 40 45

Cys Ile Trp Pro Ile Phe Phe Phe Lys Lys Lys Met Gln Arg Cys
 50 55 60

<210> 377

<211> 38

<212> PRT

<213> Homo sapiens

<400> 377

Met Thr Met Val Leu Cys Ile Phe Ile Leu Gly His His Ala Arg Glu
 1 5 10 15

Asp Pro Pro Ser Asn Gly His Ile Thr Ser Glu Gly Ala Phe Leu Val
 20 25 30

Asn Val Gly Ala Pro Gln
 35

<210> 378

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (45)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 378

Met Leu Arg Leu Glu Ala Arg Ala Thr Thr Pro Gly Leu Gln Thr His
 1 5 10 15

242

Ser Cys Leu Gly Phe Tyr Ile Lys Tyr Glu His Lys Asn Thr Phe Pro
 20 25 30

Lys Tyr Ser Leu Trp Leu Cys Leu Thr Leu Gly Thr Xaa Pro Ser Thr
 35 40 45

Ser Ser Ile Leu Arg Tyr Val Arg Gly Val Tyr Arg Gly Leu Glu Tyr
 50 55 60

Ile Arg Phe Phe Ser Asn Ser Ser Ser Ser Arg Arg Arg Leu Thr Thr
 65 70 75 80

Ser Leu Gly Phe Lys Val Ser Gly Leu Lys Phe Pro Pro Glu Ile Thr
 85 90 95

Ile Arg

<210> 379
 <211> 15
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (15)
 <223> Xaa equals stop translation

<400> 379
 Thr Leu Thr Ser Phe Leu Glu Leu Pro Leu Ala Pro Glu Pro Xaa
 1 5 10 15

<210> 380
 <211> 34
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals stop translation

<400> 380
 Met His Arg Tyr Ile Thr Phe Phe Lys Cys Phe Arg Ser Val Ile Leu
 1 5 10 15

Asp Leu Leu Phe Ile Leu Ser Pro Leu Ser Gln Gly Cys Phe Ile Leu
 20 25 30

Phe Xaa

<210> 381
 <211> 66
 <212> PRT

243

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (62)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 381

Met	Phe	Gly	Phe	Ile	Phe	Leu	Leu	Leu	Ile	Phe	Cys	Ile	Xaa	Leu	Cys
1					5				10					15	

Ser	Arg	Thr	Leu	Ser	Thr	Phe	Ile	Pro	Lys	Leu	Val	Gly	Phe	Leu	Tyr
			20					25					30		

Trp	Lys	Phe	Ser	Ile	Asn	Leu	Ser	Leu	Leu	Leu	Thr	Leu	Ile	Lys	Lys
		35					40					45			

Lys	Lys	Lys	Lys	Lys	Lys	Thr	Pro	Arg	Gly	Gly	Pro	Gly	Xaa	Gln	Ser
	50					55					60				

Pro	Pro
65	

<210> 382

<211> 317

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (207)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 382

Met	Pro	Gly	Leu	Gly	Arg	Pro	Arg	Gln	Ala	Arg	Trp	Thr	Leu	Met	Leu
1				5					10					15	

Leu	Leu	Ser	Thr	Ala	Met	Tyr	Gly	Ala	His	Ala	Pro	Leu	Leu	Ala	Leu
			20					25				30			

Cys	His	Val	Asp	Gly	Arg	Val	Pro	Phe	Arg	Pro	Ser	Ser	Ala	Val	Leu
		35					40					45			

Leu	Thr	Glu	Leu	Thr	Lys	Leu	Leu	Leu	Cys	Ala	Phe	Ser	Leu	Leu	Val
	50					55					60				

Gly	Trp	Gln	Ala	Trp	Pro	Gln	Gly	Pro	Pro	Pro	Trp	Arg	Gln	Ala	Ala
65					70					75				80	

Pro	Phe	Ala	Leu	Ser	Ala	Leu	Leu	Tyr	Gly	Ala	Asn	Asn	Asn	Leu	Val
				85					90					95	

244

Ile Tyr Leu Gln Arg Tyr Met Asp Pro Ser Thr Tyr Gln Val Leu Ser
 100 105 110
 Asn Leu Lys Ile Gly Ser Thr Ala Val Leu Tyr Cys Leu Cys Leu Arg
 115 120 125
 His Arg Leu Ser Val Arg Gln Gly Leu Ala Leu Leu Leu Leu Met Ala
 130 135 140
 Ala Gly Ala Cys Tyr Ala Ala Gly Gly Leu Gln Val Pro Gly Asn Thr
 145 150 155 160
 Leu Pro Ser Pro Pro Pro Ala Ala Ala Ala Ser Pro Met Pro Leu His
 165 170 175
 Ile Thr Pro Leu Gly Leu Leu Leu Leu Ile Leu Tyr Cys Leu Ile Ser
 180 185 190
 Gly Leu Ser Ser Val Tyr Thr Glu Leu Leu Met Lys Arg Gln Xaa Leu
 195 200 205
 Pro Leu Ala Leu Gln Asn Leu Phe Leu Tyr Thr Phe Gly Val Leu Leu
 210 215 220
 Asn Leu Gly Leu His Ala Gly Gly Gly Ser Gly Pro Gly Leu Leu Glu
 225 230 235 240
 Gly Phe Ser Gly Trp Ala Ala Leu Val Val Leu Ser Gln Ala Leu Asn
 245 250 255
 Gly Leu Leu Met Ser Ala Val Met Lys His Gly Ser Ser Ile Thr Arg
 260 265 270
 Leu Phe Val Val Ser Cys Ser Leu Val Val Asn Ala Val Leu Ser Ala
 275 280 285
 Val Leu Leu Arg Leu Gln Leu Thr Ala Ala Phe Phe Leu Ala Thr Leu
 290 295 300
 Leu Ile Gly Leu Ala Met Arg Leu Tyr Tyr Gly Ser Arg
 305 310 315

<210> 383

<211> 31

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (20)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (23)

<223> Xaa equals any of the naturally occurring L-amino acids

245

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals stop translation

 <400> 383
 Met Gly Glu Gln Pro His Phe Ser Leu Cys Val Leu Leu Ala Ala Val
 1 5 10 15
 Arg Glu Asp Xaa Asp Pro Xaa Val Phe Pro Cys Cys Phe Leu Xaa
 20 25 30

<210> 384
 <211> 43
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (43)
 <223> Xaa equals stop translation

 <400> 384
 Met Ser Phe Ile Ala Leu His Pro Leu Leu Pro Glu Ala Ala Leu Gly
 1 5 10 15
 Val Pro Gly Gln Ser Pro His Arg Pro Leu Trp Gln Thr Gln Cys Cys
 20 25 30
 Val Ala Pro Pro Gln Pro Arg Ala Glu Phe Xaa
 35 40

<210> 385
 <211> 255
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (255)
 <223> Xaa equals stop translation

 <400> 385
 Met Val Thr Ala Leu Thr Leu Leu Ala Phe Pro Leu Leu Leu Leu His
 1 5 10 15
 Ala Glu Arg Ile Ser Leu Val Phe Leu Leu Leu Phe Leu Gln Ser Phe
 20 25 30
 Leu Leu Leu His Leu Leu Ala Ala Gly Ile Pro Val Thr Thr Pro Gly
 35 40 45
 Pro Phe Thr Val Pro Trp Gln Ala Val Ser Ala Trp Ala Leu Met Ala
 50 55 60
 Thr Gln Thr Phe Tyr Ser Thr Gly His Gln Pro Val Phe Pro Ala Ile

246

65		70		75		80
His Trp His Ala Ala Phe Val Gly Phe Pro Glu Gly His Gly Ser Cys						
	85			90		95
Thr Trp Leu Pro Ala Leu Leu Val Gly Ala Asn Thr Phe Ala Ser His						
	100		105		110	
Leu Leu Phe Ala Val Gly Cys Pro Leu Leu Leu Leu Trp Pro Phe Leu						
	115		120		125	
Cys Glu Ser Gln Gly Leu Arg Lys Arg Gln Gln Pro Pro Gly Asn Glu						
	130		135		140	
Ala Asp Ala Arg Val Arg Pro Glu Glu Glu Glu Glu Pro Leu Met Glu						
	145		150		155	160
Met Arg Leu Arg Asp Ala Pro Gln His Phe Tyr Ala Ala Leu Leu Gln						
		165		170		175
Leu Gly Leu Lys Tyr Leu Phe Ile Leu Gly Ile Gln Ile Leu Ala Cys						
	180		185		190	
Ala Leu Ala Ala Ser Ile Leu Arg Arg His Leu Met Val Trp Lys Val						
	195		200		205	
Phe Ala Pro Lys Phe Ile Phe Glu Ala Val Gly Phe Ile Val Ser Ser						
	210		215		220	
Val Gly Leu Leu Leu Gly Ile Ala Leu Val Met Arg Val Asp Gly Ala						
	225		230		235	240
Val Ser Ser Trp Phe Arg Gln Leu Phe Leu Ala Gln Gln Arg Xaa						
	245		250		255	

<210> 386

<211> 20

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (20)

<223> Xaa equals stop translation

<400> 386

Met Xaa Gly Pro Trp Gly Glu Glu Ala Leu Ile Arg Leu Pro Thr Pro
1 5 10 15

Ser Gly Leu Xaa
20

247

<210> 387
 <211> 64
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (6)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (64)
 <223> Xaa equals stop translation

<400> 387
 Met Ala Thr Leu Glu Xaa Asn Gln Arg Glu Val Asp Arg Glu Ile Arg
 1 5 10 15
 Ser Leu Leu Leu Trp Phe Leu Leu Cys Glu Ile Val Ser Gly Trp Leu
 20 25 30
 Cys Pro Glu Gly Pro Trp Phe Ser Gln Gly Cys Gln Ile Tyr Lys Asn
 35 40 45
 Leu Ser Ser Ser Ser Tyr Asn Leu Ser Phe Leu Leu Ser Leu Xaa
 50 55 60

<210> 388
 <211> 40
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (40)
 <223> Xaa equals stop translation

<400> 388
 Met Ile His Ser Gly Cys Thr Ser Gln Cys Leu Glu Gly Phe Phe Leu
 1 5 10 15
 Ile Phe Leu Leu Asp Phe Asn Pro Val Leu Ala Leu Asp Leu Ile Gly
 20 25 30
 Ile Met Arg Lys Ala Ser His Xaa
 35 40

<210> 389
 <211> 35
 <212> PRT
 <213> Homo sapiens

248

<220>
 <221> SITE
 <222> (35)
 <223> Xaa equals stop translation

 <400> 389
 Met Val Phe Ser Ala Arg Val Ser Leu Tyr Thr Arg Phe Lys Val Ile
 1 5 10 15

 Leu Leu Ser Leu Leu Ile Met Ile Leu His Val Cys Trp Val Trp Val
 20 25 30

 Ile Leu Xaa
 35

<210> 390
 <211> 11
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (11)
 <223> Xaa equals stop translation

<400> 390
 Gly Leu Leu Tyr Ile Met Tyr Cys Asn Ile Xaa
 1 5 10

<210> 391
 <211> 64
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (64)
 <223> Xaa equals stop translation

<400> 391
 Met Asn Asn Gly Leu Leu Gln Gln Pro Ser Ala Leu Met Leu Leu Pro
 1 5 10 15

 Cys Arg Pro Val Leu Thr Ser Val Ala Leu Asn Ala Asn Phe Val Ser
 20 25 30

 Trp Lys Ser Arg Thr Lys Tyr Thr Ile Thr Pro Val Lys Met Arg Lys
 35 40 45

 Ser Gly Gly Arg Asp His Thr Gly Gly Asn Lys Asp Arg Gly Ile Xaa
 50 55 60

249

<210> 392
<211> 19
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (19)
<223> Xaa equals stop translation

<400> 392
Met Arg Lys Gln Arg Leu Val Pro Met Tyr Leu Gly Leu Ile Tyr Ile
1 5 10 15

Leu Leu Xaa

<210> 393
<211> 43
<212> PRT
<213> Homo sapiens

<400> 393
Met Glu Ile Ser Val Ile Lys Ile Phe Gln Asp Glu Thr Thr Leu Lys
1 5 10 15

Ile Lys Leu Cys Leu Val Ser Leu Ser Ser Leu Leu Val Ser Leu Leu
20 25 30

Leu Leu Ile Leu Pro Glu Ser Thr Ser Leu Trp
35 40

<210> 394
<211> 17
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals stop translation

<400> 394
Leu Leu Leu Pro Val Leu Ala Ser Ser Val Pro Ser His Ser Ala Thr
1 5 10 15

Xaa

<210> 395
<211> 84
<212> PRT
<213> Homo sapiens

250

<220>
 <221> SITE
 <222> (84)
 <223> Xaa equals stop translation

 <400> 395
 Met Leu Pro Leu Leu Leu Phe Thr Tyr Leu Asn Ser Phe Leu His Gln
 1 5 10 15

 Arg Ile Pro Gln Ser Val Arg Ile Leu Gly Ser Leu Val Ala Ile Leu
 20 25 30

 Leu Val Phe Leu Ile Thr Ala Ile Leu Val Lys Val Gln Leu Asp Ala
 35 40 45

 Leu Pro Phe Phe Val Ile Thr Met Ile Lys Ile Val Leu Ile Asn Ser
 50 55 60

 Phe Gly Ala Ile Leu Gln Gly Ser Leu Phe Gly Leu Ala Gly Leu Leu
 65 70 75 80

 Pro Ala Ser Xaa

<210> 396
 <211> 21
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (19)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (21)
 <223> Xaa equals stop translation

<400> 396
 Met Lys Leu Ser Leu Phe Leu Ile Leu Ser Asp Val Phe Tyr Leu Gly
 1 5 10 15

 Ser Pro Xaa Thr Xaa
 20

<210> 397
 <211> 29
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (29)
 <223> Xaa equals stop translation

251

<400> 397

Met Gly Thr Arg Arg Lys Gly Val Ala Trp Leu Ser Leu Ala Pro Leu
1 5 10 15

Ile Thr Gly Leu Ala Pro Ala His Ile Thr Ala Val Xaa
20 25

<210> 398

<211> 34

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals stop translation

<400> 398

Met Lys Asp Leu Leu Gln Arg Asn Pro Trp Lys Asn Ser Leu Leu Leu
1 5 10 15

Leu Gln Val Cys Gln Ala Phe Leu Val Cys Ser Leu Thr Gln Leu Ala
20 25 30

Val Xaa

<210> 399

<211> 47

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals stop translation

<400> 399

Met Ser Glu Ser His Lys Ile Trp Trp Cys Tyr Arg His Leu Ala Phe
1 5 10 15

Pro Leu Leu Thr Leu Ile Leu Tyr Pro Ala Thr Leu Gly Arg Ser Val
20 25 30

Phe Cys His Asp Cys Lys Phe Pro Glu Ala Ser Pro Ala Met Xaa
35 40 45

<210> 400

<211> 25

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (21)

252

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (25)

<223> Xaa equals stop translation

<400> 400

Met	Leu	Asn	Arg	Ile	Met	Val	Ala	Ser	Phe	Gly	Ala	Val	Leu	Val	Gln
1					5					10				15	

Val	Cys	Arg	Gly	Xaa	Gly	Gln	Gly	Xaa
			20				25	

<210> 401

<211> 68

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (68)

<223> Xaa equals stop translation

<400> 401

Met	Gln	Leu	Leu	Leu	Leu	Gly	Leu	Ile	Arg	Ser	Gln	Pro	Ser	Pro	Pro
1				5					10					15	

Pro	Ser	Leu	Cys	Leu	Met	Leu	Cys	Pro	Cys	Leu	Pro	Cys	Leu	Arg	Tyr
			20					25					30		

Ser	Pro	Phe	Val	Pro	Gln	His	Pro	Cys	Pro	Leu	Pro	Leu	Asp	Leu	Cys
		35					40					45			

Leu	Ala	Gly	Cys	Ser	Ser	Leu	Ser	Val	Gln	Asp	Lys	Cys	Ser	Trp	Pro
	50					55					60				

Tyr	Pro	Ile	Xaa
			65

<210> 402

<211> 85

<212> PRT

<213> Homo sapiens

<400> 402

Met	Lys	Asp	Ser	Leu	Cys	Arg	Val	Ser	Phe	Leu	Lys	Asn	Gln	Ile	Phe
1					5					10				15	

Leu	Ser	Tyr	Ile	Thr	Leu	Val	Leu	Ile	Gly	His	Ala	His	Phe	Ser	Gly
			20					25					30		

Val	Pro	His	Tyr	Asn	Val	Ser	Phe	Val	Leu	Arg	Ile	Asn	Leu	Gln	Lys
		35					40					45			

His	Leu	Lys	Ile	Thr	Thr	Ser	Asn	Gly	Ile	Glu	Ser	Lys	Lys	Thr	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

253

50 55 60

Glu Arg Gly Glu Thr Met Phe Phe Arg Thr Arg Gly Ser Thr His Ala
 65 70 75 80

Ser Ala Asp Ala Trp
 85

<210> 403

<211> 82

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 403

Met Gly Gly Ser Leu Leu Pro Gln Val Ser Ala Ala Val Leu Xaa Leu
 1 5 10 15

Asp Gly Leu Leu Leu Pro Gly Leu Lys Gly Cys Gly Pro Leu Arg Val
 20 25 30

Ser Phe Pro Gln Ala Lys Phe Lys Ala Ala Ala Leu Cys Glu Ala Leu
 35 40 45

Leu Ala Leu Gly Trp Arg Glu Asn Phe Lys Leu Phe Cys Ser Gln Gly
 50 55 60

Arg Gly Met Gly Pro Gly Cys Arg Cys Pro His Ser Ala Asn Glu Ser
 65 70 75 80

Phe Val

<210> 404

<211> 286

<212> PRT

<213> Homo sapiens

<400> 404

Met Ala Met Glu Gly Tyr Trp Arg Phe Leu Ala Leu Leu Gly Ser Ala
 1 5 10 15

Leu Leu Val Gly Phe Leu Ser Val Ile Phe Ala Leu Val Trp Val Leu
 20 25 30

His Tyr Arg Glu Gly Leu Gly Trp Asp Gly Ser Ala Leu Glu Phe Asn
 35 40 45

Trp His Pro Val Leu Met Val Thr Gly Phe Val Phe Ile Gln Gly Ile
 50 55 60

Ala Ile Ile Val Tyr Arg Leu Pro Trp Thr Trp Lys Cys Ser Lys Leu

254

65		70		75		80
Leu Met Lys Ser	Ile His Ala Gly	Leu Asn Ala Val	Ala Ala Ile Leu			
	85	90	95			
Ala Ile Ile Ser	Val Val Ala Val	Phe Glu Asn His	Asn Val Asn Asn			
	100	105	110			
Ile Ala Asn Met	Tyr Ser Leu His	Ser Trp Val Gly	Leu Ile Ala Val			
	115	120	125			
Ile Cys Tyr Leu	Leu Gln Leu Leu	Ser Gly Phe Ser	Val Phe Leu Leu			
	130	135	140			
Pro Trp Ala Pro	Leu Ser Leu Arg	Ala Phe Leu Met	Pro Ile His Val			
	145	150	155	160		
Tyr Ser Gly Ile	Val Ile Phe Gly	Thr Val Ile Ala	Thr Ala Leu Met			
	165	170	175			
Gly Leu Thr Glu	Lys Leu Ile Phe	Ser Leu Arg Asp	Pro Ala Tyr Ser			
	180	185	190			
Thr Phe Pro Pro	Glu Gly Val Phe	Val Asn Thr Leu	Gly Leu Leu Ile			
	195	200	205			
Leu Val Phe Gly	Ala Leu Ile Phe	Trp Ile Val Thr	Arg Pro Gln Trp			
	210	215	220			
Lys Arg Pro Lys	Glu Pro Asn Ser	Thr Ile Leu His	Pro Asn Gly Gly			
	225	230	235	240		
Thr Glu Gln Gly	Ala Arg Gly Ser	Met Pro Ala Tyr	Ser Gly Asn Asn			
	245	250	255			
Met Asp Lys Ser	Asp Ser Glu Leu	Asn Ser Glu Val	Ala Ala Arg Lys			
	260	265	270			
Arg Asn Leu Ala	Leu Asp Glu Ala	Gly Gln Arg Ser	Thr Met			
	275	280	285			

<210> 405

<211> 154

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
 <222> (83)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (103)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (110)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (121)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (123)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (126)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (134)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (154)
 <223> Xaa equals stop translation

 <400> 405
 Met Thr Lys Ala Arg Leu Phe Arg Leu Trp Leu Val Leu Gly Ser Val
 1 5 10 15
 Phe Met Ile Leu Leu Ile Ile Val Tyr Trp Asp Ser Ala Gly Ala Ala
 20 25 30
 His Phe Tyr Leu His Thr Ser Phe Ser Arg Pro His Thr Gly Pro Pro
 35 40 45
 Leu Pro Thr Pro Gly Pro Asp Arg Asp Arg Glu Leu Thr Ala Asp Ser
 50 55 60
 Asp Val Asp Xaa Phe Leu Asp Xaa Phe Leu Ser Ala Gly Val Lys Gln
 65 70 75 80
 Ser Asp Xaa Pro Arg Lys Glu Thr Glu Gln Pro Pro Ala Pro Gly Ser
 85 90 95

256

Met Glu Glu Ser Val Arg Xaa Tyr Asp Trp Ser Pro Arg Xaa Ala Arg
 100 105 110

Arg Thr Gln Thr Arg Ala Gly Ser Xaa Arg Xaa Gly Gly Xaa Cys Cys
 115 120 125

Gly Ala Ser Ala Pro Xaa Pro Ala Trp Pro Ser Pro Pro Arg Ser Ala
 130 135 140

His Ser Thr Thr Ser Pro Thr Arg Ser Xaa
 145 150

<210> 406
 <211> 37
 <212> PRT
 <213> Homo sapiens

<400> 406
 Met Leu Leu Leu Ile Val Leu Val Ala Asn Ile Leu Ser Met Ser Asn
 1 5 10 15

Met Ser Asn Ala Val Val Ser Asp Leu His Ile Leu Val His Leu Ile
 20 25 30

Ser His Lys Ala Asn
 35

<210> 407
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 407
 Met Cys Ile His Val Phe Met Ser Val Leu Trp Val Leu Phe Leu Leu
 1 5 10 15

Asn Pro Leu Cys Thr Gly Leu Trp Pro Leu Val Asn Cys Phe Ser Val
 20 25 30

Leu Arg His Ala Asp Trp Val Leu Gly Ala Asp Tyr Lys Gly Glu Glu
 35 40 45

Leu Asn Arg His Gln Gly Pro Met Lys Pro Lys Asp
 50 55 60

<210> 408
 <211> 447
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (447)
 <223> Xaa equals stop translation

257

<400> 408

Met Leu Leu Gly Leu Leu Met Ala Ala Cys Phe Thr Phe Cys Leu Ser
 1 5 10 15
 His Gln Asn Leu Lys Glu Phe Ala Leu Thr Asn Pro Glu Lys Ser Ser
 20 25 30
 Thr Lys Glu Thr Glu Arg Lys Glu Thr Lys Ala Glu Glu Glu Leu Asp
 35 40 45
 Ala Glu Val Leu Glu Val Phe His Pro Thr His Glu Trp Gln Ala Leu
 50 55 60
 Gln Pro Gly Gln Ala Val Pro Ala Gly Ser His Val Arg Leu Asn Leu
 65 70 75 80
 Gln Thr Gly Glu Arg Glu Ala Lys Leu Gln Tyr Glu Asp Lys Phe Arg
 85 90 95
 Asn Asn Leu Lys Gly Lys Arg Leu Asp Ile Asn Thr Asn Thr Tyr Thr
 100 105 110
 Ser Gln Asp Leu Lys Ser Ala Leu Ala Lys Phe Lys Glu Gly Ala Glu
 115 120 125
 Met Glu Ser Ser Lys Glu Asp Lys Ala Arg Gln Ala Glu Val Lys Arg
 130 135 140
 Leu Phe Arg Pro Ile Glu Glu Leu Lys Lys Asp Phe Asp Glu Leu Asn
 145 150 155 160
 Val Val Ile Glu Thr Asp Met Gln Ile Met Val Arg Leu Ile Asn Lys
 165 170 175
 Phe Asn Ser Ser Ser Ser Ser Leu Glu Glu Lys Ile Ala Ala Leu Phe
 180 185 190
 Asp Leu Glu Tyr Tyr Val His Gln Met Asp Asn Ala Gln Asp Leu Leu
 195 200 205
 Ser Phe Gly Gly Leu Gln Val Val Ile Asn Gly Leu Asn Ser Thr Glu
 210 215 220
 Pro Leu Val Lys Glu Tyr Ala Ala Phe Val Leu Gly Ala Ala Phe Ser
 225 230 235 240
 Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly Ala Leu Gln
 245 250 255
 Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr Ala Lys Lys
 260 265 270
 Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe Pro Tyr Ala
 275 280 285
 Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val Leu Arg Thr Leu
 290 295 300

258

Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val Arg Val Val Thr Leu
305 310 315 320

Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu Glu Ala Glu
325 330 335

Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr Arg Gln Val
340 345 350

His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp Cys Glu Ile Thr Ala
355 360 365

His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys Val Leu Gln
370 375 380

Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp Arg Tyr Arg Gln Asp
385 390 395 400

Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln Ala Glu Tyr Gln Val
405 410 415

Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp Glu Gly Tyr Phe Gln
420 425 430

Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys Glu Leu Arg Xaa
435 440 445

<210> 409

<211> 64

<212> PRT

<213> Homo sapiens

<400> 409

Met Leu Tyr Ser Asp Leu Lys Leu Val Arg Cys His Asn Gly Pro Val
1 5 10 15

His Val Ile Ser Val Tyr Thr Thr Pro Pro Asp Pro Ser Asn Pro Tyr
20 25 30

Asn Thr Pro Pro Leu Phe Ala Ser Cys Met Val Ile Ser Tyr Val Thr
35 40 45

Phe Thr Pro Val Ser Ala Asp Cys Phe Phe Asn Val Leu Val Cys Phe
50 55 60

<210> 410

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

259

<223> Xaa equals stop translation

<400> 410

Glu Leu Leu Phe Leu Leu Ile Ile Ile Leu Gly Glu Ser Leu Ser Asp
1 5 10 15

Val Ile Leu Leu Ile Cys Phe Xaa
20

<210> 411

<211> 35

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals stop translation

<400> 411

Met Phe Tyr Trp Gly Gly Leu Ser Phe Tyr Phe Leu Leu Ser Ser Gly
1 5 10 15

Val Gly Phe Tyr Cys Phe Leu Phe Gly Phe Gly Met Glu Ile Trp Ile
20 25 30

Ala Ala Xaa
35

<210> 412

<211> 41

<212> PRT

<213> Homo sapiens

<400> 412

Met Gly Lys Val Gly Trp Leu Met Val Gly Gly Val Ala Pro Gly Ile
1 5 10 15

Arg Gly Gly Trp Gly Trp Thr Leu Gly Ile Met Val Gly Gly Ala Ile
20 25 30

Ala His Cys Cys Cys Cys Leu Ile Arg
35 40

<210> 413

<211> 25

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals stop translation

<400> 413

260

Met Lys Leu Ser Leu Leu Ile Leu Thr Leu Met Gln Arg Tyr Phe Arg
 1 5 10 15

Thr Ile Thr Asn Ser Leu Cys Lys Xaa
 20 25

<210> 414
 <211> 79
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (79)
 <223> Xaa equals stop translation

<400> 414
 Met Pro Ala Val Ser Gly Pro Gly Pro Leu Phe Cys Leu Leu Leu Leu
 1 5 10 15

Leu Leu Asp Pro His Ser Pro Glu Thr Gly Cys Pro Pro Leu Arg Arg
 20 25 30

Phe Glu Tyr Lys Leu Ser Phe Lys Gly Pro Arg Leu Ala Leu Pro Gly
 35 40 45

Ala Gly Ile Pro Phe Trp Ser His His Gly Gly Glu Gly Gln Gly Trp
 50 55 60

Gly Pro Leu Cys Pro Gly Ser Leu Lys Val Leu Glu Gly Leu Xaa
 65 70 75

<210> 415
 <211> 51
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (20)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (28)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 415
 Met His Tyr Leu Leu Lys Glu Cys Asp Ile Asp Thr Asp Ala Tyr Phe
 1 5 10 15

Phe Phe Phe Xaa Leu Leu Val Leu Phe Leu Pro Xaa Lys Tyr Ser Pro
 20 25 30

Pro Phe Tyr Ser Ile Val Leu Phe Arg Trp Asn Asp Ser Tyr Lys Ile
 35 40 45

261

Ser His Tyr
50

<210> 416

<211> 257

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (100)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 416

Met Ala Ala Leu Thr Ser His Leu Gln Asn Gln Ser Asn Asn Ser Asn
1 5 10 15

Trp Asn Leu Arg Thr Arg Ser Lys Cys Lys Lys Asp Val Phe Met Pro
20 25 30

Pro Ser Ser Ser Ser Glu Leu Gln Glu Ser Arg Gly Leu Ser Asn Phe
35 40 45

Thr Ser Thr His Leu Leu Leu Lys Glu Asp Glu Gly Val Asp Asp Val
50 55 60

Asn Phe Arg Lys Val Arg Lys Pro Lys Gly Lys Val Thr Ile Leu Lys
65 70 75 80

Gly Ile Pro Ile Lys Lys Thr Lys Lys Gly Cys Arg Lys Ser Cys Ser
85 90 95

Gly Phe Val Xaa Ser Asp Ser Lys Arg Glu Ser Val Cys Asn Lys Ala
100 105 110

Asp Ala Glu Ser Glu Pro Val Ala Gln Lys Ser Gln Leu Asp Arg Thr
115 120 125

Val Cys Ile Ser Asp Ala Gly Ala Cys Gly Glu Thr Leu Ser Val Thr
130 135 140

Ser Glu Glu Asn Ser Leu Val Lys Lys Lys Glu Arg Ser Leu Ser Ser
145 150 155 160

Gly Ser Asn Phe Cys Ser Glu Gln Lys Thr Ser Gly Ile Ile Asn Lys
165 170 175

Phe Cys Ser Ala Lys Asp Ser Glu His Asn Glu Lys Tyr Glu Asp Thr
180 185 190

Phe Leu Glu Ser Glu Glu Ile Gly Thr Lys Val Glu Val Val Glu Arg
195 200 205

Lys Glu His Leu His Thr Asp Ile Leu Lys Arg Gly Ser Glu Met Asp
210 215 220

262

Asn Asn Cys Ser Pro Thr Arg Lys Asp Phe Thr Glu Asp Thr Ile Pro
 225 230 235 240

Arg Asn Thr Asp Arg Lys Lys Glu Asn Lys Pro Val Phe Phe Gln Gln
 245 250 255

Ile

<210> 417

<211> 424

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (144)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (263)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 417

Met Glu Lys Gln Cys Cys Ser His Pro Val Ile Cys Ser Leu Ser Thr
 1 5 10 15

Met Tyr Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser Ser
 20 25 30

Arg Ile Leu Leu Val Lys Tyr Ser Ala Asn Glu Glu Asn Lys Tyr Asp
 35 40 45

Tyr Leu Pro Thr Thr Val Asn Val Cys Ser Glu Leu Val Lys Leu Val
 50 55 60

Phe Cys Val Leu Val Ser Phe Cys Val Ile Lys Lys Asp His Gln Ser
 65 70 75 80

Arg Asn Leu Lys Tyr Ala Ser Trp Lys Glu Phe Ser Asp Phe Met Lys
 85 90 95

Trp Ser Ile Pro Ala Phe Leu Tyr Phe Leu Asp Asn Leu Ile Val Phe
 100 105 110

Tyr Val Leu Ser Tyr Leu Gln Pro Ala Met Ala Val Ile Phe Ser Asn
 115 120 125

Phe Ser Ile Ile Thr Thr Ala Leu Leu Phe Arg Ile Val Leu Lys Xaa
 130 135 140

Arg Leu Asn Trp Ile Gln Trp Ala Ser Leu Leu Thr Leu Phe Leu Ser
 145 150 155 160

Ile Val Ala Leu Thr Ala Gly Thr Lys Thr Leu Gln His Asn Leu Ala
 165 170 175

263

Gly Arg Gly Phe His His Asp Ala Phe Phe Ser Pro Ser Asn Ser Cys
 180 185 190
 Leu Leu Phe Arg Asn Glu Cys Pro Arg Lys Asp Asn Cys Thr Ala Lys
 195 200 205
 Glu Trp Thr Phe Pro Glu Ala Lys Trp Asn Thr Thr Ala Arg Val Phe
 210 215 220
 Ser His Ile Arg Leu Gly Met Gly His Val Leu Ile Ile Val Gln Cys
 225 230 235 240
 Phe Ile Ser Ser Met Ala Asn Ile Tyr Asn Glu Lys Ile Leu Lys Glu
 245 250 255
 Gly Asn Gln Leu Thr Glu Xaa Ile Phe Ile Gln Asn Ser Lys Leu Tyr
 260 265 270
 Phe Phe Gly Ile Leu Phe Asn Gly Leu Thr Leu Gly Leu Gln Arg Ser
 275 280 285
 Asn Arg Asp Gln Ile Lys Asn Cys Gly Phe Phe Tyr Gly His Ser Ala
 290 295 300
 Phe Ser Val Ala Leu Ile Phe Val Thr Ala Phe Gln Gly Leu Ser Val
 305 310 315 320
 Ala Phe Ile Leu Lys Phe Leu Asp Asn Met Phe His Val Leu Met Ala
 325 330 335
 Gln Val Thr Thr Val Ile Ile Thr Thr Val Ser Val Leu Val Phe Asp
 340 345 350
 Phe Arg Pro Ser Leu Glu Phe Phe Leu Glu Ala Pro Ser Val Leu Leu
 355 360 365
 Ser Ile Phe Ile Tyr Asn Ala Ser Lys Pro Gln Val Pro Glu Tyr Ala
 370 375 380
 Pro Arg Gln Glu Arg Ile Arg Asp Leu Ser Gly Asn Leu Trp Glu Arg
 385 390 395 400
 Ser Ser Gly Asp Gly Glu Glu Leu Glu Arg Leu Thr Lys Pro Lys Ser
 405 410 415
 Asp Glu Ser Asp Glu Asp Thr Phe
 420

<210> 418

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

264

<223> Xaa equals stop translation

<400> 418

Met	Trp	Gly	Gln	Gly	Ser	Gln	Lys	Ser	His	Phe	Ser	Asp	Leu	Val	Phe
1				5					10					15	

Gly	Val	Arg	Glu	Leu	Cys	Ala	Gln	Pro	Ser	Asp	Pro	Gly	Ser	Pro	His
			20					25					30		

Xaa

<210> 419

<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (80)

<223> Xaa equals stop translation

<400> 419

Met	Val	Gln	His	Ile	Gln	Pro	Ala	Ala	Leu	Ser	Leu	Leu	Ala	Gln	Trp
1				5					10					15	

Ser	Thr	Leu	Val	Gln	Glu	Leu	Glu	Ala	Ala	Leu	Gln	Leu	Ala	Phe	Tyr
			20					25					30		

Pro	Asp	Ala	Val	Glu	Glu	Trp	Leu	Glu	Glu	Asn	Val	His	Pro	Ser	Leu
		35					40					45			

Gln	Arg	Leu	Gln	Xaa	Leu	Leu	Gln	Asp	Leu	Ser	Glu	Val	Ser	Ala	Pro
	50					55					60				

Pro	Leu	Pro	Pro	Thr	Ser	Pro	Gly	Arg	Asp	Val	Ala	Gln	Asp	Pro	Xaa
	65					70				75					80

<210> 420

<211> 95

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (82)

<223> Xaa equals any of the naturally occurring L-amino acids

265

<220>
 <221> SITE
 <222> (83)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (95)
 <223> Xaa equals stop translation

 <400> 420
 Met Leu Asn Gln Gly Tyr Ile Arg Lys Ile Ile Leu Ile Ile Ile Leu
 1 5 10 15
 Gly Ser Phe Ser Ser Pro Lys Lys Ala Ile Leu Met Gly Phe Gln Asn
 20 25 30
 Gln Lys Lys Ala Leu Asn Glu Glu Gln Thr Thr Gly Val Pro Met Ser
 35 40 45
 Ile Ser Gly Lys Leu Arg Pro Ser Arg Ser Leu Asp Phe Val Gln Pro
 50 55 60
 Pro Arg Phe Gln Ser Gln Gln Pro Ser Ala Val Val Asp Arg Arg Gly
 65 70 75 80
 Phe Xaa Xaa Lys Ala Ala Arg Gly Gln Glu Phe Ser Glu Ser Xaa
 85 90 95

 <210> 421
 <211> 257
 <212> PRT
 <213> Homo sapiens

 <400> 421
 Met Arg Gly Pro Ala Gln Ala Lys Leu Leu Pro Gly Ser Ala Ile Gln
 1 5 10 15
 Ala Leu Val Gly Leu Ala Arg Pro Leu Val Leu Ala Leu Leu Leu Val
 20 25 30
 Ser Ala Ala Leu Ser Ser Val Val Ser Arg Thr Asp Ser Pro Ser Pro
 35 40 45
 Thr Val Leu Asn Ser His Ile Ser Thr Pro Asn Val Asn Ala Leu Thr
 50 55 60
 His Glu Asn Gln Thr Lys Pro Ser Ile Ser Gln Ile Ser Thr Thr Leu
 65 70 75 80
 Pro Pro Thr Thr Ser Thr Lys Lys Ser Gly Gly Ala Ser Val Val Pro
 85 90 95
 His Pro Ser Pro Thr Pro Leu Ser Gln Glu Glu Ala Asp Asn Asn Glu
 100 105 110
 Asp Pro Ser Ile Glu Glu Glu Asp Leu Leu Met Leu Asn Ser Ser Pro

266

115	120	125
Ser Thr Ala Lys Asp Thr Leu Asp Asn Gly Asp Tyr Gly Glu Pro Asp		
130	135	140
Tyr Asp Trp Thr Thr Gly Pro Arg Asp Asp Asp Glu Ser Asp Asp Thr		
145	150	155
Leu Glu Glu Asn Arg Gly Tyr Met Glu Ile Glu Gln Ser Val Lys Ser		
	165	170
		175
Phe Lys Met Pro Ser Ser Asn Ile Glu Glu Glu Asp Ser His Phe Phe		
	180	185
		190
Phe His Leu Ile Ile Phe Ala Phe Cys Ile Ala Val Val Tyr Ile Thr		
	195	200
		205
Tyr His Asn Lys Arg Lys Ile Phe Leu Leu Val Gln Ser Arg Lys Trp		
210	215	220
Arg Asp Gly Leu Cys Ser Lys Thr Val Glu Tyr His Arg Leu Asp Gln		
225	230	235
		240
Asn Val Asn Glu Ala Met Pro Ser Leu Lys Ile Thr Asn Asp Tyr Ile		
	245	250
		255

Phe

<210> 422

<211> 704

<212> PRT

<213> Homo sapiens

<400> 422

Met Trp Tyr Arg Leu Arg Leu Leu Lys Pro Gln Pro Asn Ile Ile Pro		
1	5	10
		15
Thr Val Lys Lys Ile Val Leu Leu Ala Gly Trp Ala Leu Phe Leu Phe		
	20	25
		30
Leu Ala Tyr Lys Val Ser Lys Thr Asp Arg Glu Tyr Gln Glu Tyr Asn		
	35	40
		45
Pro Tyr Glu Val Leu Asn Leu Asp Pro Gly Ala Thr Val Ala Glu Ile		
	50	55
		60
Lys Lys Gln Tyr Arg Leu Leu Ser Leu Lys Tyr His Pro Asp Lys Gly		
65	70	75
		80
Gly Asp Glu Val Met Phe Met Arg Ile Ala Lys Ala Tyr Ala Ala Leu		
	85	90
		95
Thr Asp Glu Glu Ser Arg Lys Asn Trp Glu Glu Phe Gly Asn Pro Asp		
	100	105
		110
Gly Pro Gln Ala Thr Ser Phe Gly Ile Ala Leu Pro Ala Trp Ile Val		

267

115	120	125
Asp Gln Lys Asn Ser Ile 130	Leu Val Leu Leu Val 135	Tyr Gly Leu Ala Phe 140
Met Val Ile Leu Pro Val 145	Val Val Gly Ser Trp 150	Trp Tyr Arg Ser Ile 155 160
Arg Tyr Ser Gly Asp Gln Ile 165	Leu Ile Arg Thr Thr 170	Gln Ile Tyr Thr 175
Tyr Phe Val Tyr Lys Thr 180	Arg Asn Met Asp Met 185	Lys Arg Leu Ile Met 190
Val Leu Ala Gly Ala Ser 195	Glu Phe Asp Pro Gln 200	Tyr Asn Lys Asp Ala 205
Thr Ser Arg Pro Thr Asp 210	Asn Ile Leu Ile Pro 215	Gln Leu Ile Arg Glu 220
Ile Gly Ser Ile Asn Leu Lys 225	Lys Asn Glu Pro Pro 230	Leu Thr Cys Pro 235 240
Tyr Ser Leu Lys Ala Arg 245	Val Leu Leu Leu Ser 250	His Leu Ala Arg Met 255
Lys Ile Pro Glu Thr Leu 260	Glu Glu Asp Gln Gln 265	Phe Met Leu Lys Lys 270
Cys Pro Ala Leu Leu Gln 275	Glu Met Val Asn Val 280	Ile Cys Gln Leu Ile 285
Val Met Ala Arg Asn Arg 290	Glu Glu Arg Glu Phe 295	Arg Ala Pro Thr Leu 300
Ala Ser Leu Glu Asn Cys 305	Met Lys Leu Ser Gln 310	Met Ala Val Gln Gly 315 320
Leu Gln Gln Phe Lys Ser 325	Pro Leu Leu Gln Leu 330	Pro His Ile Glu Glu 335
Asp Asn Leu Arg Arg Val 340	Ser Asn His Lys Lys 345	Tyr Lys Ile Lys Thr 350
Ile Gln Asp Leu Val Ser 355	Leu Lys Glu Ser Asp 360	Arg His Thr Leu Leu 365
His Phe Leu Glu Asp Glu 370	Lys Tyr Glu Glu Val 375	Met Ala Val Leu Gly 380
Ser Phe Pro Tyr Val Thr 385	Met Asp Ile Lys Ser 390	Gln Val Leu Asp Asp 395 400
Glu Asp Ser Asn Asn Ile 405	Thr Val Gly Ser Leu 410	Val Thr Val Leu Val 415
Lys Leu Thr Arg Gln Thr 420	Met Ala Glu Val Phe 425	Glu Lys Glu Gln Ser 430

268

Ile Cys Ala Ala Glu Glu Gln Pro Ala Glu Asp Gly Gln Gly Glu Thr
 435 440 445
 Asn Lys Asn Arg Thr Lys Gly Gly Trp Gln Gln Lys Ser Lys Gly Pro
 450 455 460
 Lys Lys Thr Ala Lys Ser Lys Lys Lys Lys Pro Leu Lys Lys Lys Pro
 465 470 475 480
 Thr Pro Val Leu Leu Pro Gln Ser Lys Gln Gln Lys Gln Lys Gln Ala
 485 490 495
 Asn Gly Val Val Gly Asn Glu Ala Ala Val Lys Glu Asp Glu Glu Glu
 500 505 510
 Val Ser Asp Lys Gly Ser Asp Ser Glu Glu Glu Glu Thr Asn Arg Asp
 515 520 525
 Ser Gln Ser Glu Lys Asp Asp Gly Ser Asp Arg Asp Ser Asp Arg Glu
 530 535 540
 Gln Asp Glu Lys Gln Asn Lys Asp Asp Glu Ala Glu Trp Gln Glu Leu
 545 550 555 560
 Gln Gln Ser Ile Gln Arg Lys Glu Arg Ala Leu Leu Glu Thr Lys Ser
 565 570 575
 Lys Ile Thr His Pro Val Tyr Ser Leu Tyr Phe Pro Glu Glu Lys Gln
 580 585 590
 Glu Trp Trp Trp Leu Tyr Ile Ala Asp Arg Lys Glu Gln Thr Leu Ile
 595 600 605
 Ser Met Pro Tyr His Val Cys Thr Leu Lys Asp Thr Glu Glu Val Glu
 610 615 620
 Leu Lys Phe Pro Ala Pro Gly Lys Pro Gly Asn Tyr Gln Tyr Thr Val
 625 630 635 640
 Phe Leu Arg Ser Asp Ser Tyr Met Gly Leu Asp Gln Ile Lys Pro Leu
 645 650 655
 Lys Leu Glu Val His Glu Ala Lys Pro Val Pro Glu Asn His Pro Gln
 660 665 670
 Trp Asp Thr Ala Ile Glu Gly Asp Glu Asp Gln Glu Asp Ser Glu Gly
 675 680 685
 Phe Glu Asp Ser Phe Glu Glu Glu Glu Glu Glu Glu Glu Asp Asp Asp
 690 695 700

<210> 423

<211> 190

269

<212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (29)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 423
 Met Lys Ala Ser Gln Cys Cys Cys Cys Leu Ser His Leu Leu Ala Ser
 1 5 10 15
 Val Leu Leu Leu Leu Leu Leu Pro Glu Leu Ser Gly Xaa Leu Xaa Val
 20 25 30
 Leu Leu Gln Ala Ala Glu Ala Ala Pro Gly Leu Gly Pro Pro Asp Pro
 35 40 45
 Arg Pro Arg Thr Leu Pro Pro Leu Pro Pro Gly Pro Thr Pro Ala Gln
 50 55 60
 Gln Pro Gly Arg Gly Leu Ala Glu Ala Ala Gly Pro Arg Gly Ser Glu
 65 70 75 80
 Gly Gly Asn Gly Ser Asn Pro Val Ala Gly Leu Glu Thr Asp Asp His
 85 90 95
 Gly Gly Lys Ala Gly Glu Gly Ser Val Gly Gly Gly Leu Ala Val Ser
 100 105 110
 Pro Asn Pro Gly Asp Lys Pro Met Thr Gln Arg Ala Leu Thr Val Leu
 115 120 125
 Met Val Val Ser Gly Ala Val Leu Val Tyr Phe Val Val Arg Thr Val
 130 135 140
 Arg Met Arg Arg Arg Asn Arg Lys Thr Arg Arg Tyr Gly Val Leu Asp
 145 150 155 160
 Thr Asn Ile Glu Asn Met Glu Leu Thr Pro Leu Glu Gln Asp Asp Glu
 165 170 175
 Asp Asp Asp Asn Thr Leu Phe Asp Ala Asn His Pro Arg Arg
 180 185 190

<210> 424
 <211> 179
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE

270

<222> (179)

<223> Xaa equals stop translation

<400> 424

Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile
 1 5 10 15

Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser
 20 25 30

Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
 35 40 45

Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
 50 55 60

Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
 65 70 75 80

Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Lys Ser Thr Lys
 85 90 95

Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
 100 105 110

Pro Ser Thr Asp Val Gln Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly
 115 120 125

Phe His Glu Asp Asp Pro Phe Phe Tyr Asp Glu His Thr Leu Arg Lys
 130 135 140

Arg Gly Leu Leu Val Ala Ala Val Leu Phe Ile Thr Gly Ile Ile Ile
 145 150 155 160

Leu Thr Ser Gly Lys Cys Arg Gln Leu Ser Arg Leu Cys Arg Asn His
 165 170 175

Cys Arg Xaa

<210> 425

<211> 40

<212> PRT

<213> Homo sapiens

<400> 425

Met Phe Lys Cys Leu Gln Thr Thr Phe Leu Phe Ile Leu Asp Phe Thr
 1 5 10 15

Trp Glu Ser Lys Val Gln Phe His Lys Ala Ser Val Tyr Leu Ser Leu
 20 25 30

Ser Ile Tyr Ile Asp Cys His Ala
 35 40

<210> 426

271

<211> 232

<212> PRT

<213> Homo sapiens

<400> 426

Met Leu Ala Gly Lys Leu Ile Pro Val His Gln Val Arg Gly Leu Lys
 1 5 10 15
 Glu Lys Ile Val Arg Ser Phe Glu Val Ser Pro Asp Gly Ser Phe Leu
 20 25 30
 Leu Ile Asn Gly Ile Ala Gly Tyr Leu His Leu Leu Ala Met Lys Thr
 35 40 45
 Lys Glu Leu Ile Gly Ser Met Lys Ile Asn Gly Arg Val Ala Ala Ser
 50 55 60
 Thr Phe Ser Ser Asp Ser Lys Lys Val Tyr Ala Ser Ser Gly Asp Gly
 65 70 75 80
 Glu Val Tyr Val Trp Asp Val Asn Ser Arg Lys Cys Leu Asn Arg Phe
 85 90 95
 Val Asp Glu Gly Ser Leu Tyr Gly Leu Ser Ile Ala Thr Ser Arg Asn
 100 105 110
 Gly Gln Tyr Val Ala Cys Gly Ser Asn Cys Gly Val Val Asn Ile Tyr
 115 120 125
 Asn Gln Asp Ser Cys Leu Gln Glu Thr Asn Pro Lys Pro Ile Lys Ala
 130 135 140
 Ile Met Asn Leu Val Thr Gly Val Thr Ser Leu Thr Phe Asn Pro Thr
 145 150 155 160
 Thr Glu Ile Leu Ala Ile Ala Ser Glu Lys Met Lys Glu Ala Val Arg
 165 170 175
 Leu Val His Leu Pro Ser Cys Thr Val Phe Ser Asn Phe Pro Val Ile
 180 185 190
 Lys Asn Lys Asn Ile Ser His Val His Thr Met Asp Phe Ser Pro Arg
 195 200 205
 Ser Gly Tyr Phe Ala Leu Gly Asn Glu Lys Gly Lys Ala Leu Met Tyr
 210 215 220
 Arg Leu His His Tyr Ser Asp Phe
 225 230

<210> 427

<211> 250

<212> PRT

<213> Homo sapiens

<400> 427

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val

1					5					10						15	
Gly	Gly	Glu	Thr	Arg	Ile	Ile	Lys	Gly	Phe	Glu	Cys	Lys	Pro	His	Ser		
			20					25					30				
Gln	Pro	Trp	Gln	Ala	Ala	Leu	Phe	Glu	Lys	Thr	Arg	Leu	Leu	Cys	Gly		
		35					40					45					
Ala	Thr	Leu	Ile	Ala	Pro	Arg	Trp	Leu	Leu	Thr	Ala	Ala	His	Cys	Leu		
	50					55					60						
Lys	Pro	Arg	Tyr	Ile	Val	His	Leu	Gly	Gln	His	Asn	Leu	Gln	Lys	Glu		
65					70					75					80		
Glu	Gly	Cys	Glu	Gln	Thr	Arg	Thr	Ala	Thr	Glu	Ser	Phe	Pro	His	Pro		
				85					90					95			
Gly	Phe	Asn	Asn	Ser	Leu	Pro	Asn	Lys	Asp	His	Arg	Asn	Asp	Ile	Met		
		100						105					110				
Leu	Val	Lys	Met	Ala	Ser	Pro	Val	Ser	Ile	Thr	Trp	Ala	Val	Arg	Pro		
		115					120					125					
Leu	Thr	Leu	Ser	Ser	Arg	Cys	Val	Thr	Ala	Gly	Thr	Ser	Cys	Leu	Ile		
	130					135					140						
Ser	Gly	Trp	Gly	Ser	Thr	Ser	Ser	Pro	Gln	Leu	Arg	Leu	Pro	His	Thr		
145					150					155					160		
Leu	Arg	Cys	Ala	Asn	Ile	Thr	Ile	Ile	Glu	His	Gln	Lys	Cys	Glu	Asn		
				165					170					175			
Ala	Tyr	Pro	Gly	Asn	Ile	Thr	Asp	Thr	Met	Val	Cys	Ala	Ser	Val	Gln		
			180					185					190				
Glu	Gly	Gly	Lys	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Val		
		195					200					205					
Cys	Asn	Gln	Ser	Leu	Gln	Gly	Ile	Ile	Ser	Trp	Gly	Gln	Asp	Pro	Cys		
	210					215					220						
Ala	Ile	Thr	Arg	Lys	Pro	Gly	Val	Tyr	Thr	Lys	Val	Cys	Lys	Tyr	Val		
225					230					235					240		
Asp	Trp	Ile	Gln	Glu	Thr	Met	Lys	Asn	Asn								
				245					250								

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<210> 428
<211> 58
<212> PRT
<213> Homo sapiens
```

```

<400> 428
Met Trp Thr Lys Asn Asp Lys Leu Lys Lys Phe Phe Phe Leu Arg Tyr
  1             5             10             15
Leu Gln Asn Met Val Tyr Phe Tyr Val Glu Lys Lys Ser Tyr Glu Gly

```

20

30

Met Thr Ala Cys Phe Ser Ile Ile Leu Ala
50 55

```
<210> 429
<211> 219
<212> PRT
<213> Homo sapiens
```

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<220>
<221> SITE
<222> (61)
<223> Xaa equals any of the naturally occurring L-amino acids

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<220>  
<221> SITE  
<222> (105)  
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<220> .
<221> SITE
<222> (117)
<223> Xaa equals any of the naturally occurring L-amino acids

```

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<220>
<221> SITE
<222> (219)
<223> Xaa equals stop translation
```

<400> 429
Met Ala Val Val Leu Leu Ala Asn Leu Ala Gln Gly Asp Ser Leu Ala
1 5 10 15

Ala Arg Ala Ile Ala Val Gln Lys Gly Ser Ile Gly Asn Leu Leu Gly
20 25 30

Phe Leu Glu Asp Ser Leu Ala Ala Thr Gln Phe Gln Gln Ser Gln Ala
35 40 45

Ser Leu Leu His Met Gln Asn Pro Pro Phe Glu Pro Xaa Ser Val Asp
50 55 60

Met Met Arg Arg Ala Ala Arg Ala Leu Leu Ala Leu Ala Lys Val Asp
65 70 75 80

Glu Asn His Ser Glu Phe Thr Leu Tyr Glu Ser Arg Leu Leu Asp Ile
85 90 95

Ser Val Ser Pro Leu Met Asn Ser Xaa Val Ser Gln Val Ile Cys Asp
100 105 110

Val Leu Phe Leu Xaa Trp Pro Val Met Thr Ala Val Gly His Leu Pro
115 120 125

274

Pro Pro Cys Val Cys Ala Cys Val Glu Asn Leu Glu Thr Asp Cys Cys
 130 135 140

Pro Leu Phe Met Gln Asn His Leu Arg Ile Gln Phe Thr Leu Cys Cys
 145 150 155 160

Pro Ala Ser Pro Leu Gly Lys Ser Leu Ser Cys Phe Ser Leu Leu Leu
 165 170 175

Pro Pro Pro Leu Pro Pro Ser Pro His Ala Phe Leu Phe Leu Val Leu
 180 185 190

Thr Leu Leu Pro Ser Gly Pro Tyr Pro Thr Leu Phe Glu Lys Thr Lys
 195 200 205

Leu Cys Leu His Arg Arg Leu Phe Leu Phe Xaa
 210 215

<210> 430
 <211> 51
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (51)
 <223> Xaa equals stop translation

<400> 430
 Met Leu Pro Asp Glu Ser Phe Gly Leu Leu Leu Ser Ile Pro Ser Leu
 1 5 10 15

Thr Pro Ser Ala Ala Ala Pro Ser Phe Cys Val His Leu Met Gln Ala
 20 25 30

Ser Arg Ser Ser Lys Arg Ala Ser His Val Pro Val His Leu Leu Trp
 35 40 45

Gly Asp Xaa
 50

<210> 431
 <211> 50
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (27)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (50)
 <223> Xaa equals stop translation

275

<400> 431

Met Arg Pro Gly Ser Phe Ser Phe Ile Ala Phe Leu Ala Thr Glu Val
 1 5 10 15

Ser Ser Cys Phe Pro Gly Arg Pro Asp Cys Xaa Thr Gly Met Trp Leu
 20 25 30

Leu Gln Leu Gln Lys Lys Gln Arg Thr Leu Leu Ala Met Ala Pro Arg
 35 40 45

Arg Xaa
 50

<210> 432

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (55)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (70)

<223> Xaa equals stop translation

<400> 432

Asp Arg Pro Cys Pro Ser Ser Leu Trp Lys Val Phe Pro Leu Leu Leu
 1 5 10 15

Leu Leu Met Arg Leu Phe Pro Leu Pro Val Pro Gly Asn Gln Arg Ala
 20 25 30

Xaa Leu Pro His Pro Phe Xaa Ala Pro Arg Leu Pro Cys Leu Leu Cys
 35 40 45

Leu Cys Thr Gln Gln Phe Xaa Val Cys Ser His Tyr Leu Pro Ala Gly
 50 55 60

Tyr Arg Val Asn Ser Xaa
 65 70

<210> 433

276

<211> 40
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (40)
 <223> Xaa equals stop translation

<400> 433
 Met His Glu Lys Ala Trp Asn Leu Ile Leu Leu Trp Trp Leu Ser Leu
 1 5 10 15
 Asp Leu Leu Gly Val Ala Lys Thr Ala Met Trp Ala Gln Trp Cys Gly
 20 25 30
 Leu Asn Asp His Lys Gly Lys Xaa
 35 40

<210> 434
 <211> 104
 <212> PRT
 <213> Homo sapiens

<400> 434
 Met Ala Phe Val Leu Leu Phe Cys Phe Val Gly Leu Gln Ser Ser Arg
 1 5 10 15
 Ala Gly Pro Tyr Ser Glu Leu Val Leu Cys Gln Thr Pro Ala Ser Ala
 20 25 30
 Pro Asp Pro Val Ser Thr Leu Cys Val Leu Glu Glu Glu Pro Leu Asp
 35 40 45
 Ala Tyr Pro Asp Ser Pro Ser Ala Cys Leu Val Leu Asn Trp Glu Glu
 50 55 60
 Pro Cys Asn Asn Gly Ser Glu Ile Leu Ala Tyr Thr Ile Asp Leu Gly
 65 70 75 80
 Asp Thr Ser Ile Thr Val Gly Asn Thr Thr Met His Val Met Lys Asp
 85 90 95
 Leu Leu Pro Glu Thr Thr Tyr Arg
 100

<210> 435
 <211> 38
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (38)
 <223> Xaa equals stop translation

277

<400> 435

Met Phe Ser Leu Leu Trp Leu Val Cys Val Pro Ser Asn Ser Ser Val
1 5 10 15

Ala Asn Val Thr Ala Ser Arg Gly Gly Val Phe Lys Arg Ser Leu Gly
20 25 30

His Glu Gly Phe Ser Xaa
35

<210> 436

<211> 35

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals stop translation

<400> 436

Lys Trp Leu Leu Phe Ile Phe Leu Leu Cys Leu Gln Leu Val Asn Ala
1 5 10 15

Leu Leu Ser Leu Phe Gln Glu Arg Phe Val His Cys Pro Ala Arg Phe
20 25 30

Val Ser Xaa
35

<210> 437

<211> 32

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (32)

<223> Xaa equals stop translation

<400> 437

Met Leu Leu Phe Leu Ser Ile Thr Asn Ser Leu Ser Phe Ile Ser Val
1 5 10 15

Asp Lys Pro Phe Gly Gln Ser Glu Asp Val Cys Pro Val Ile Ser Xaa
20 25 30

<210> 438

<211> 127

<212> PRT

<213> Homo sapiens

278

<220>
 <221> SITE
 <222> (127)
 <223> Xaa equals stop translation

 <400> 438
 Met Glu Phe Leu Phe Asn Lys Thr Gly Trp Ala Phe Ala Ala Leu Cys
 1 5 10 15
 Phe Val Leu Ala Met Thr Ser Gly Gln Met Trp Asn His Ile Arg Gly
 20 25 30
 Pro Pro Tyr Ala His Lys Asn Pro His Thr Gly His Val Asn Tyr Ile
 35 40 45
 His Gly Ser Ser Gln Ala Gln Phe Val Ala Glu Thr His Ile Val Leu
 50 55 60
 Leu Phe Asn Gly Gly Val Thr Leu Gly Met Val Leu Leu Cys Glu Ala
 65 70 75 80
 Ala Thr Ser Asp Met Asp Ile Gly Lys Arg Lys Ile Met Cys Val Ala
 85 90 95
 Gly Ile Gly Leu Val Val Leu Phe Phe Ser Trp Met Leu Ser Ile Phe
 100 105 110
 Arg Ser Lys Tyr His Gly Tyr Pro Tyr Ser Phe Leu Met Ser Xaa
 115 120 125

<210> 439
 <211> 69
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (10)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (69)
 <223> Xaa equals stop translation

<400> 439
 Met Thr Trp His Ser Arg Glu Ser Phe Xaa Leu Leu Arg Val Val Ala
 1 5 10 15
 Pro Ser Gln Ala Pro Gly Met Gln Val Ser Pro Ser Gln Arg Ala Trp
 20 25 30
 Arg Arg Pro Leu His Arg Cys His Val Ala Ala Pro Arg Pro His His
 35 40 45
 Phe Ala Phe Phe Arg Asn Pro Phe Ser Trp Ser Phe Ile Lys Leu Leu
 50 55 60

279

Tyr Arg Tyr Leu Xaa
65

<210> 440

<211> 92

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (92)

<223> Xaa equals stop translation

<400> 440

Met Gly Leu Lys Leu Asn Gly Arg Tyr Ile Ser Leu Ile Leu Ala Val
1 5 10 15

Gln Ile Ala Tyr Leu Val Gln Ala Val Arg Ala Ala Gly Lys Cys Asp
20 25 30

Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp Thr
35 40 45

Trp Pro Thr Thr Arg Ser Leu Gly Arg Gln Asp Glu His Gln Asp Arg
50 55 60

Val His Ile Leu Gly Gly Phe Pro Gln Leu His Gly His Ser Pro Tyr
65 70 75 80

Gly Leu Pro Gly Arg Gly Glu Arg Tyr Val Gly Xaa
85 90

<210> 441

<211> 380

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (264)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (296)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (380)

<223> Xaa equals stop translation

<400> 441

Met Ala Arg Arg Ser Ala Phe Pro Ala Ala Ala Leu Trp Leu Trp Ser
1 5 10 15

280

Ile Leu Leu Cys Leu Leu Ala Leu Arg Ala Glu Ala Gly Pro Pro Gln
 20 25 30
 Glu Glu Ser Leu Tyr Leu Trp Ile Asp Ala His Gln Ala Arg Val Leu
 35 40 45
 Ile Gly Phe Glu Glu Asp Ile Leu Ile Val Ser Glu Gly Lys Met Ala
 50 55 60
 Pro Phe Thr His Asp Phe Arg Lys Ala Gln Gln Arg Met Pro Ala Ile
 65 70 75 80
 Pro Val Asn Ile His Ser Met Asn Phe Thr Trp Gln Ala Ala Gly Gln
 85 90 95
 Ala Glu Tyr Phe Tyr Glu Phe Leu Ser Leu Arg Ser Leu Asp Lys Gly
 100 105 110
 Ile Met Ala Asp Pro Thr Val Asn Val Pro Leu Leu Gly Thr Val Pro
 115 120 125
 His Lys Ala Ser Val Val Gln Val Gly Phe Pro Cys Leu Gly Lys Gln
 130 135 140
 Asp Gly Val Ala Ala Phe Glu Val Asp Val Ile Val Met Asn Ser Glu
 145 150 155 160
 Gly Asn Thr Ile Leu Gln Thr Pro Gln Asn Ala Ile Phe Phe Lys Thr
 165 170 175
 Cys Gln Gln Ala Glu Cys Pro Gly Gly Cys Arg Asn Gly Gly Phe Cys
 180 185 190
 Asn Glu Arg Arg Ile Cys Glu Cys Pro Asp Gly Phe His Gly Pro His
 195 200 205
 Cys Glu Lys Ala Leu Cys Thr Pro Arg Cys Met Asn Gly Gly Leu Cys
 210 215 220
 Val Thr Pro Gly Phe Cys Ile Cys Pro Pro Gly Phe Tyr Gly Val Asn
 225 230 235 240
 Cys Asp Lys Ala Asn Cys Ser Thr Thr Cys Phe Asn Gly Gly Thr Cys
 245 250 255
 Phe Tyr Pro Gly Lys Cys Ile Xaa Pro Pro Gly Leu Glu Gly Glu Gln
 260 265 270
 Cys Glu Ile Ser Lys Cys Pro Gln Pro Cys Arg Asn Gly Gly Lys Cys
 275 280 285
 Ile Gly Lys Ser Lys Cys Lys Xaa Ser Lys Gly Tyr Gln Gly Asp Leu
 290 295 300
 Cys Ser Lys Pro Val Cys Glu Pro Gly Cys Gly Ala His Gly Thr Cys
 305 310 315 320

281

His Glu Pro Asn Lys Cys Gln Cys Gln Glu Gly Trp His Gly Arg His
 325 330 335
 Cys Asn Lys Arg Tyr Glu Ala Ser Leu Ile His Ala Leu Arg Pro Ala
 340 345 350
 Gly Ala Gln Leu Arg Gln His Thr Pro Ser Leu Lys Lys Ala Glu Glu
 355 360 365
 Arg Arg Asp Pro Pro Glu Ser Asn Tyr Ile Trp Xaa
 370 375 380

<210> 442

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (21)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (23)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (24)

<223> Xaa equals stop translation

<400> 442

Met Thr Ser Asn Leu Leu Leu Leu Thr Leu Leu Leu Lys Asp Thr Leu
 1 5 10 15

Xaa Leu Ala Lys Xaa Asn Xaa Xaa
 20

<210> 443

<211> 47

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

282

<222> (47)

<223> Xaa equals stop translation

<400> 443

Met Arg His His Thr Gln Leu Asn Phe Ile Phe Leu Val Glu Met Val
 1 5 10 15

Phe Leu His Val Gly Gln Ala Gly Leu Lys Leu Pro Thr Ser Gly Asp
 20 25 30

Xaa Ala Cys Phe Gly Leu Pro Lys Val Leu Gly Leu Gln Ala Xaa
 35 40 45

<210> 444

<211> 214

<212> PRT

<213> Homo sapiens

<400> 444

Met Gln Val Thr Ile Thr Leu Thr Ser Pro Ile Ile Arg Glu Glu Asn
 1 5 10 15

Met Arg Glu Gly Asp Val Thr Ser Gly Met Val Lys Asp Pro Pro Asp
 20 25 30

Val Leu Asp Arg Gln Lys Cys Leu Asp Ala Leu Ala Ala Leu Arg His
 35 40 45

Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Gln Ser Cys Val Ile
 50 55 60

Ile Ile Arg Ile Leu Arg Asp Leu Cys Gln Arg Val Pro Thr Trp Ser
 65 70 75 80

Asp Phe Pro Ser Trp Ala Met Glu Leu Leu Val Glu Lys Ala Ile Ser
 85 90 95

Ser Ala Ser Ser Pro Gln Ser Pro Gly Asp Ala Leu Arg Arg Val Phe
 100 105 110

Glu Cys Ile Ser Ser Gly Ile Ile Leu Lys Gly Ser Pro Gly Leu Leu
 115 120 125

Asp Pro Cys Glu Lys Asp Pro Phe Asp Thr Leu Ala Thr Met Thr Asp
 130 135 140

Gln Gln Arg Glu Asp Ile Thr Ser Ser Ala Gln Phe Ala Leu Arg Leu
 145 150 155 160

Leu Ala Phe Arg Gln Ile His Lys Val Leu Gly Met Asp Pro Leu Pro
 165 170 175

Gln Met Ser Gln Arg Phe Asn Ile His Asn Asn Arg Lys Arg Arg Arg
 180 185 190

Asp Ser Asp Gly Val Asp Gly Phe Glu Ala Glu Gly Lys Lys Asp Lys
 195 200 205

283

Lys Asp Tyr Asp Asn Phe
210

<210> 445

<211> 144

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (144)

<223> Xaa equals stop translation

<400> 445

Leu Leu Ser Ile Leu Leu Cys Leu Leu Ala Ser Gly Leu Val Val Phe
1 5 10 15

Phe Leu Phe Pro His Ser Val Leu Val Asp Asp Asp Gly Ile Lys Val
20 25 30

Val Lys Val Thr Phe Asn Lys Gln Asp Ser Leu Val Ile Leu Thr Ile
35 40 45

Met Ala Thr Leu Lys Ile Arg Asn Ser Asn Phe Tyr Thr Val Ala Val
50 55 60

Thr Ser Leu Ser Ser Gln Ile Gln Tyr Met Asn Thr Val Val Asn Phe
65 70 75 80

Thr Gly Lys Ala Glu Met Gly Gly Pro Phe Ser Tyr Val Tyr Phe Phe
85 90 95

Cys Thr Val Pro Glu Ile Leu Val His Asn Ile Val Ile Phe Met Arg
100 105 110

Thr Ser Val Lys Ile Ser Tyr Ile Gly Leu Met Thr Gln Ser Ser Leu
115 120 125

Glu Thr His His Tyr Val Asp Cys Gly Gly Asn Ser Thr Ala Ile Xaa
130 135 140

<210> 446

<211> 37

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> Xaa equals stop translation

<400> 446

284

Met Phe Phe Phe Leu Tyr Val Tyr Ser Val Leu Cys Gly Leu Leu Val
 1 5 10 15

Tyr Pro Ser Leu Pro Ser His Ser Val Ser Leu Val Thr Ser Leu Val
 20 25 30

Ala Ser Ala Leu Xaa
 35

<210> 447

<211> 37

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals stop translation

<400> 447

Met Ala Ser Ile Asn Ala Val Tyr Ile His Val Phe Leu Gly Val Cys
 1 5 10 15

Val Gln Ala Thr Ala Ala Cys Pro Trp Cys Ser Gln Cys Arg Xaa Gly
 20 25 30

Ser Val Pro Ser Xaa
 35

<210> 448

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (192)

<223> Xaa equals stop translation

<400> 448

Met Met Ala Ala Met Val Leu Thr Ser Leu Ser Cys Ser Pro Val Val
 1 5 10 15

Gln Ser Pro Pro Gly Thr Glu Ala Asn Phe Ser Ala Ser Arg Ala Ala
 20 25 30

285

Cys Asp Pro Trp Lys Glu Ser Gly Asp Ile Ser Asp Ser Gly Xaa Ser
 35 40 45
 Thr Thr Ser Gly His Trp Ser Gly Ser Ser Gly Val Ser Thr Pro Ser
 50 55 60
 Pro Pro His Pro Gln Ala Ser Pro Lys Tyr Leu Gly Asp Ala Phe Gly
 65 70 75 80
 Ser Pro Gln Thr Asp His Gly Phe Glu Thr Asp Pro Asp Pro Phe Leu
 85 90 95
 Leu Asp Glu Pro Ala Pro Arg Lys Arg Lys Asn Ser Val Lys Val Met
 100 105 110
 Tyr Lys Cys Leu Trp Pro Asn Cys Gly Lys Val Leu Arg Ser Ile Val
 115 120 125
 Gly Ile Lys Arg His Val Lys Ala Leu His Leu Gly Asp Thr Val Asp
 130 135 140
 Ser Asp Gln Phe Lys Arg Glu Glu Asp Phe Tyr Tyr Thr Glu Val Gln
 145 150 155 160
 Leu Lys Glu Glu Ser Ala Ala Ala Ala Ala Ala Ala Ala Asp Pro
 165 170 175
 Gln Ser Leu Gly Leu Pro Pro Pro Ser Gln Leu Pro Pro Pro Ala Xaa
 180 185 190

<210> 449

<211> 31

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals stop translation

<400> 449

Met Ser Thr Asn Tyr Leu Thr Asp Val Cys Ser Leu Phe Ser Tyr Leu
 1 5 10 15

Asn Tyr Leu Tyr Phe His His His Leu Pro Val Pro Asn Thr Xaa
 20 25 30

<210> 450

<211> 101

<212> PRT

<213> Homo sapiens

<220>

286

<221> SITE
 <222> (44)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (46)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (77)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (78)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (101)
 <223> Xaa equals stop translation

 <400> 450
 Met Gly Phe Phe Phe Val Leu Phe Phe Leu Tyr Leu Ala Leu Ser Arg
 1 5 10 15
 Asp Trp Ser Ile Asn Phe Leu Lys Asp His Arg Ile Asn Phe Phe Val
 20 25 30
 Ala Thr Ser Tyr Phe Ser Val Tyr Val Arg Gly Xaa Pro Xaa Val Pro
 35 40 45
 Ala Asp Thr Pro Leu Gly Pro Leu Leu Ser Leu Trp Leu His His Asn
 50 55 60
 Ala Phe Phe Ser Ile Leu Pro Lys Phe Pro Glu Asn Xaa Xaa Phe Leu
 65 70 75 80
 Ile Leu Lys Lys Leu Val Val Glu Met Gly Trp Asp Leu Phe Ile Ser
 85 90 95
 Pro Glu Asn Lys Xaa
 100

 <210> 451
 <211> 37
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (37)
 <223> Xaa equals stop translation

 <400> 451

287

Met Ala Arg Tyr Phe Ile Phe Phe Ile Leu Val Phe Met Lys Val Ser
 1 5 10 15
 Leu Asn Thr Thr Trp Pro Ala Pro Arg Pro Ala Thr Leu Arg Thr Ala
 20 25 30
 Asn Lys Ser Lys Xaa
 35

<210> 452
 <211> 42
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (42)
 <223> Xaa equals stop translation

<400> 452
 Phe Ser Thr Ile Arg Ser Gly Leu Thr Asp Arg Ser Val Asn Phe Leu
 1 5 10 15
 Phe Leu Phe Leu Asp Val Pro Asp Cys Arg Leu Val Asn Ile Glu Leu
 20 25 30
 Met Ala Asn Ser Thr Val Thr His Ala Xaa
 35 40

<210> 453
 <211> 48
 <212> PRT
 <213> Homo sapiens

<400> 453
 Met Ser Glu Trp Glu Leu Ser Ser Lys Phe Ser Gln Thr Gln Arg Gln
 1 5 10 15
 His Cys Leu Leu Leu Asn Asp Tyr Ser Phe Leu Pro Val Phe Trp Tyr
 20 25 30
 Phe Leu Gly Ile Leu Leu Thr Thr Ala Ile Thr Leu Phe Tyr Phe His
 35 40 45

<210> 454
 <211> 25
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (25)

288

<223> Xaa equals stop translation

<400> 454

Met Pro Trp Arg Arg Ala Gly Leu Met Met Leu Pro Ile Ile Thr Gly
1 5 10 15

Cys Cys Pro Cys Ser Ala Ser Ile Xaa
20 25

<210> 455

<211> 54

<212> PRT

<213> Homo sapiens

<400> 455

Met Tyr Leu Cys Lys Thr Val Lys Val Leu Ile Cys Tyr Asp Trp Ile
1 5 10 15

Leu Gly Leu Val Ser Ser Gly Gln His Trp Val Val Ser Leu Ser Tyr
20 25 30

Ser Ile Arg Val Tyr Pro Ala Met His Phe Thr Leu Cys Val His Ile
35 40 45

Tyr Ser Lys Glu Pro Cys
50

<210> 456

<211> 42

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (42)

<223> Xaa equals stop translation

<400> 456

Met Thr Ala Leu Val Trp Arg Lys Gly Pro Asp Gly Gly Ser Arg Lys
1 5 10 15

Pro Ile Leu Leu Leu Phe Phe Phe Leu Pro Leu Ile Leu Cys Phe His
20 25 30

Ser Phe Ile His Ser Ser Asn Ile Cys Xaa
35 40

<210> 457

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (15)

289

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (66)

<223> Xaa equals stop translation

<400> 457

Met	Phe	Leu	Thr	Thr	Trp	Phe	Leu	Leu	Leu	Ser	Val	Ala	Trp	Xaa	Ala
1				5					10					15	

Leu	Thr	Arg	Ser	Gly	Arg	Ser	Cys	Leu	Pro	Leu	Val	Gly	Arg	Pro	Arg
		20					25						30		

Glu	Gln	Ser	Pro	Arg	Thr	His	Cys	Ala	Ala	Ser	Ser	Thr	Lys	Glu	Arg
		35					40						45		

Asn	Ser	Asp	Pro	Gln	Pro	Ser	Pro	Pro	Glu	Val	Val	Gly	Pro	Leu	Trp
	50					55						60			

Ser	Xaa
65	

<210> 458

<211> 156

<212> PRT

<213> Homo sapiens

<400> 458

Met	Lys	Ala	Ile	Gly	Ile	Glu	Pro	Ser	Leu	Ala	Thr	Tyr	His	His	Ile
1				5					10					15	

Ile	Arg	Leu	Phe	Asp	Gln	Pro	Gly	Asp	Pro	Leu	Lys	Arg	Ser	Ser	Phe
		20						25					30		

Ile	Ile	Tyr	Asp	Ile	Met	Asn	Glu	Leu	Met	Gly	Lys	Arg	Phe	Ser	Pro
		35					40					45			

Lys	Asp	Pro	Asp	Asp	Asp	Lys	Phe	Phe	Gln	Ser	Ala	Met	Ser	Ile	Cys
	50					55					60				

Ser	Ser	Leu	Arg	Asp	Leu	Glu	Leu	Ala	Tyr	Gln	Val	His	Gly	Leu	Leu
65					70					75				80	

Lys	Thr	Gly	Asp	Asn	Trp	Lys	Phe	Ile	Gly	Pro	Asp	Gln	His	Arg	Asn
				85					90					95	

Phe	Tyr	Tyr	Ser	Lys	Phe	Phe	Asp	Leu	Ile	Cys	Leu	Met	Glu	Gln	Ile
			100					105					110		

Asp	Val	Thr	Leu	Lys	Trp	Tyr	Glu	Asp	Leu	Ile	Pro	Ser	Ala	Tyr	Phe
		115					120					125			

Pro	His	Ser	Gln	Thr	Met	Ile	His	Leu	Leu	Gln	Ala	Leu	Asp	Val	Ala
	130					135					140				

Asn	Arg	Leu	Glu	Val	Ile	Pro	Lys	Ile	Trp	Glu	Arg
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290

145

150

155

<210> 459

<211> 31

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals stop translation

<400> 459

Met	Asn	Asp	Asn	Ser	Pro	Asn	His	Ser	Ser	Ser	Tyr	Leu	Pro	Leu	Pro
1				5					10					15	

Leu	Thr	Ile	Val	Ile	Leu	Gln	Thr	Gly	His	Lys	Gly	Thr	Leu	Xaa
			20					25					30	

<210> 460

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (57)

<223> Xaa equals stop translation

<400> 460

Met	His	Phe	Leu	Phe	Arg	Phe	Ile	Val	Phe	Phe	Tyr	Leu	Trp	Gly	Leu
1				5					10					15	

Phe	Thr	Ala	Gln	Arg	Gln	Lys	Lys	Glu	Glu	Ser	Thr	Glu	Glu	Val	Lys
			20					25					30		

Ile	Glu	Val	Leu	His	Arg	Pro	Glu	Asn	Cys	Ser	Lys	Thr	Ser	Lys	Lys
		35					40					45			

Gly	Asp	Leu	Leu	Lys	Cys	Pro	Leu	Xaa
	50					55		

<210> 461

<211> 416

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (338)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (416)

291

<223> Xaa equals stop translation

<400> 461

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro
 1 5 10 15

Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys
 20 25 30

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg
 35 40 45

Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His
 50 55 60

Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp
 65 70 75 80

Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr
 85 90 95

Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln
 100 105 110

Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp
 115 120 125

Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu
 130 135 140

His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe
 145 150 155 160

Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr
 165 170 175

Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu
 180 185 190

Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met
 195 200 205

Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu
 210 215 220

Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met
 225 230 235 240

Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe
 245 250 255

Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn
 260 265 270

Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys
 275 280 285

Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Met

292

290	295	300
Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala Arg		
305	310	315 320
Tyr Ile Gln Thr Leu Lys Asp His Arg Pro Arg Met Val Trp Asp Ser		
	325	330 335
Gln Xaa Ser Glu His Phe Phe Glu Tyr Lys Lys Ser Arg Ser Gly Arg		
	340	345 350
His Val Val Phe Tyr Pro Thr Leu Lys Ser Leu Gln Val Arg Leu Glu		
	355	360 365
Leu Ala Arg Glu Leu Gly Val Gly Val Ser Ile Trp Glu Leu Ala Arg		
	370	375 380
Ala Trp Thr Thr Ser Thr Thr Cys Ser Arg Trp Ala Leu Arg Pro Pro		
385	390	395 400
Arg Trp Thr Cys Ser Phe Leu Ser His Gly Val Ser Glu Gln Val Xaa		
	405	410 415

<210> 462

<211> 64

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 462

Met	Ala	Pro	Gly	Pro	Leu	Ser	Ala	Thr	Gln	Ala	Val	Val	Ile	His	Thr
1				5					10					15	

Thr	His	Cys	Leu	Gln	Leu	Pro	Val	Trp	Cys	Leu	Ser	Leu	Val	Ser	Glu
			20					25					30		

Leu	Leu	Gly	Arg	Ala	Pro	Pro	His	Asn	Lys	Asp	Ala	Leu	Arg	Pro	Ser
		35					40					45			

Lys	Lys	Lys	Lys	Lys	Lys	Leu	Xaa	Gly	Gly	Pro	Val	Pro	Ile	Pro	Pro
		50				55					60				

<210> 463

<211> 206

<212> PRT

<213> Homo sapiens

293

<220>
 <221> SITE
 <222> (80)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (93)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (206)
 <223> Xaa equals stop translation

 <400> 463
 Met Leu Gly Ala Lys Pro His Trp Leu Pro Gly Pro Leu His Ser Pro
 1 5 10 15
 Gly Leu Pro Leu Val Leu Val Leu Leu Ala Leu Gly Ala Gly Trp Ala
 20 25 30
 Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val
 35 40 45
 Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu
 50 55 60
 Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Ala Ala Val Arg Ser Xaa
 65 70 75 80
 His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Xaa Gly Ala Ile
 85 90 95
 Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala
 100 105 110
 Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe
 115 120 125
 His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met
 130 135 140
 Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val
 145 150 155 160
 Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly
 165 170 175
 Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Asn Leu Leu Gly Gly Trp
 180 185 190
 Lys Tyr Ser Ser Phe Ser Gly Phe Leu Ile Phe Pro Leu Xaa
 195 200 205

<210> 464

294

<211> 38
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (38)
 <223> Xaa equals stop translation

<400> 464
 Met Gln Arg Lys Val Ser Asp Phe Ile Ile His Gln Arg Leu Thr Val
 1 5 10 15
 Asn Leu Cys Val Ile Ser Phe Phe Phe Phe Leu Pro Ile Cys Ile Phe
 20 25 30
 Ser Leu Ala Lys Lys Xaa
 35

<210> 465
 <211> 136
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (136)
 <223> Xaa equals stop translation

<400> 465
 Val Val Gly Thr Gly Thr Ser Leu Ala Leu Ser Ser Leu Leu Ser Leu
 1 5 10 15
 Leu Leu Phe Ala Gly Met Gln Met Tyr Ser Arg Gln Leu Ala Ser Thr
 20 25 30
 Glu Trp Leu Thr Ile Gln Gly Gly Leu Leu Gly Ser Gly Leu Phe Val
 35 40 45
 Phe Ser Leu Thr Ala Phe Asn Asn Leu Glu Asn Leu Val Phe Gly Lys
 50 55 60
 Gly Phe Gln Ala Lys Ile Phe Pro Glu Ile Leu Leu Cys Leu Leu Leu
 65 70 75 80
 Ala Leu Phe Ala Ser Gly Leu Ile His Arg Val Cys Val Thr Thr Cys
 85 90 95
 Phe Ile Phe Ser Met Val Gly Leu Tyr Tyr Ile Asn Lys Ile Ser Ser
 100 105 110
 Thr Leu Tyr Gln Ala Ala Ala Pro Val Leu Thr Pro Ala Lys Val Thr
 115 120 125
 Gly Lys Ser Lys Lys Arg Asn Xaa
 130 135

295

<210> 466
 <211> 50
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (18)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (25)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (50)
 <223> Xaa equals stop translation

<400> 466
 Met Cys Leu Ser Arg Trp Lys Ile Phe Tyr Thr Leu Leu Ile Leu Phe
 1 5 10 15
 Xaa Xaa Phe Ser Ile Thr Ser Glu Xaa Glu Thr Phe Tyr Met Ile Ile
 20 25 30
 Ile His His Asn Pro Thr Gln Ile Thr Ala Ser Cys Ser Phe Thr Phe
 35 40 45
 Leu Xaa
 50

<210> 467
 <211> 71
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (27)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (49)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (71)

296

<223> Xaa equals stop translation

<400> 467

Met Trp Gly Cys Ser Gly Leu Gly His Arg Thr Val Ser Phe Leu Leu
1 5 10 15

Leu Leu Pro Cys Ser Phe Pro Arg Pro Cys Xaa Leu Phe Gly Leu Ile
20 25 30

Pro Ile Ser Arg Pro Cys Lys Val Glu Ala Pro Arg Leu Ser Val Pro
35 40 45

Xaa Leu Ser Cys Ala Ser His Pro Tyr Cys Asn Cys Pro Met Ser Thr
50 55 60

Ser Cys Pro Leu Pro Arg Xaa
65 70

<210> 468

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (59)

<223> Xaa equals stop translation

<400> 468

Asp Phe Val Pro Val Leu Val Phe Val Leu Ile Lys Ala Asn Pro Pro
1 5 10 15

Cys Leu Leu Ser Thr Val Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys
20 25 30

Leu Ser Gly Glu Glu Ser Tyr Trp Trp Met Gln Phe Thr Ala Ala Val
35 40 45

Glu Phe Ile Lys Thr Ile Asp Asp Arg Lys Xaa
50 55

<210> 469

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

297

<220>
 <221> SITE
 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (38)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (46)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (59)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 469
 Met Phe Ser Arg Thr Ser Asn Phe Trp Thr Phe Phe Phe Gln Phe Leu
 1 5 10 15

Ile Phe Lys Val Phe Leu Val Leu Lys Asn Xaa Phe Thr Ser Gln Lys
 20 25 30

Ile Xaa Xaa Ile Xaa Xaa Glu Lys Pro Lys Lys Lys Lys Xaa Arg Gly
 35 40 45

Gly Arg Ala Pro Ser Pro Gln Gly Gly Pro Xaa
 50 55

<210> 470
 <211> 18
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (18)
 <223> Xaa equals stop translation

<400> 470
 Met Gly Leu Leu Ile Phe Met Leu Leu Ile Gly Ile His Ser Gln Cys
 1 5 10 15

Ser Xaa

<210> 471

298

<211> 316
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (103)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (302)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (305)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (316)
 <223> Xaa equals stop translation

<400> 471

Met	Ser	Thr	Lys	Lys	Leu	Cys	Ile	Val	Gly	Gly	Ile	Leu	Leu	Val	Phe
1				5					10					15	
Gln	Ile	Ile	Ala	Phe	Leu	Val	Gly	Gly	Leu	Ile	Ala	Pro	Gly	Pro	Thr
			20					25					30		
Thr	Ala	Val	Ser	Tyr	Met	Ser	Val	Lys	Cys	Val	Asp	Ala	Arg	Lys	Asn
		35					40					45			
His	His	Lys	Thr	Lys	Trp	Phe	Val	Pro	Trp	Gly	Pro	Asn	His	Cys	Asp
	50					55					60				
Lys	Ile	Arg	Asp	Ile	Glu	Glu	Ala	Ile	Pro	Arg	Glu	Ile	Glu	Ala	Asn
	65				70					75					80
Asp	Ile	Val	Phe	Ser	Val	His	Ile	Pro	Leu	Pro	His	Met	Glu	Met	Ser
				85					90					95	
Pro	Trp	Phe	Gln	Phe	Met	Xaa	Phe	Ile	Leu	Gln	Leu	Asp	Ile	Ala	Phe
			100					105					110		
Lys	Leu	Asn	Asn	Gln	Ile	Arg	Glu	Asn	Ala	Glu	Val	Ser	Met	Asp	Val
		115					120					125			
Ser	Leu	Ala	Tyr	Arg	Asp	Asp	Ala	Phe	Ala	Glu	Trp	Thr	Glu	Met	Ala
	130					135					140				
His	Glu	Arg	Val	Pro	Arg	Lys	Leu	Lys	Cys	Thr	Phe	Thr	Ser	Pro	Lys
	145					150				155					160
Thr	Pro	Glu	His	Gly	Gly	Pro	Val	Thr	Met	Asn	Val	Met	Ser	Phe	Leu
				165					170						175

299

Ser Trp Lys Leu Gly Leu Trp Pro Met Lys Phe Tyr Leu Leu Asn Ile
 180 185 190
 Arg Leu Pro Val Asn Glu Lys Lys Lys Ile Asn Val Gly Ile Gly Glu
 195 200 205
 Ile Lys Asp Ile Arg Leu Val Gly Ile His Gln Asn Gly Gly Phe Thr
 210 215 220
 Lys Val Trp Phe Ala Met Lys Thr Phe Leu Thr Pro Ser Ile Phe Ile
 225 230 235 240
 Ile Met Val Trp Tyr Trp Arg Arg Ile Thr Met Met Ser Arg Pro Pro
 245 250 255
 Val Leu Leu Glu Lys Val Ile Phe Ala Leu Gly Ile Ser Met Thr Phe
 260 265 270
 Ile Asn Ile Pro Val Glu Trp Phe Ser Ile Gly Phe Asp Trp Thr Trp
 275 280 285
 Met Leu Leu Phe Gly Asp Ile Arg Gln Ala Ser Ser Met Xaa Cys Phe
 290 295 300
 Xaa Pro Ser Gly Ser Ser Ser Val Ala Ser Thr Xaa
 305 310 315

<210> 472

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> Xaa equals stop translation

<400> 472

Met Leu Ala Leu Leu Gly Leu Leu Ala Gly Thr Glu His Pro Pro Gly
 1 5 10 15

Pro Gln Gly Pro Gly Pro Ser Xaa
 20

<210> 473

<211> 10

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals stop translation

<400> 473

Met Pro Ser Gly Ala Cys Cys Ser Pro Xaa

300

1 5 10

<210> 474
 <211> 85
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (36)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (44)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (85)
 <223> Xaa equals stop translation

<400> 474
 Tyr Val Met Ile Phe Lys Lys Glu Phe Ala Pro Ser Asp Glu Glu Leu
 1 5 10 15

Asp Ser Tyr Arg Arg Gly Glu Glu Trp Asp Pro Gln Lys Ala Glu Glu
 20 25 30

Lys Arg Asn Xaa Lys Glu Leu Ala Gln Arg Gln Xaa Gly Gly Gly Ser
 35 40 45

Pro Ala Gly Ala Cys Gly Gly Glu Pro Cys Gln Arg Leu Gln Gly Gln
 50 55 60

Val Gln Pro Pro His Arg Gln Gly Ser Ser Gln Arg Arg Ser Pro His
 65 70 75 80

Ala Thr Gly Gln Xaa
 85

<210> 475
 <211> 26
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (26)
 <223> Xaa equals stop translation

<400> 475
 Met Leu Pro Ala Leu Ser Thr Val Leu Leu Pro Thr Pro Ser Leu Cys
 1 5 10 15

Ser Gly Asn Pro Arg Glu Gly Trp Ala Xaa

301

20

25

<210> 476
 <211> 34
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals stop translation

<400> 476
 Lys Glu Phe Phe Val Phe Leu Phe Val Cys Leu Phe Trp Leu Leu Ser
 1 5 10 15

Asn Thr Pro Leu Thr Phe Ile Ser Ile Ile Leu Gln Arg Lys Glu Thr
 20 25 30

Asn Xaa

<210> 477
 <211> 172
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (151)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (172)
 <223> Xaa equals stop translation

<400> 477
 Met Tyr Ser Leu His Ser Trp Val Gly Leu Ile Ala Val Ile Cys Tyr
 1 5 10 15

Leu Leu Gln Leu Leu Ser Gly Phe Ser Val Phe Leu Leu Pro Trp Ala
 20 25 30

Pro Leu Ser Leu Arg Ala Phe Leu Met Pro Ile His Val Tyr Ser Gly
 35 40 45

Ile Val Ile Phe Gly Thr Val Ile Ala Thr Ala Leu Met Gly Leu Thr
 50 55 60

Glu Lys Leu Ile Phe Ser Leu Arg Asp Pro Ala Tyr Ser Thr Phe Pro
 65 70 75 80

Pro Glu Gly Val Phe Val Asn Thr Leu Gly Leu Leu Ile Leu Val Phe
 85 90 95

302

Gly Ala Leu Ile Phe Trp Ile Val Thr Arg Pro Gln Trp Lys Arg Pro
 100 105 110

Lys Glu Pro Asn Ser Thr Ile Leu His Pro Asn Gly Gly Thr Glu Gln
 115 120 125

Gly Ala Arg Gly Ser Met Pro Ala Tyr Ser Gly Asn Asn Met Asp Lys
 130 135 140

Ser Asp Ser Glu Leu Asn Xaa Glu Val Ala Ala Arg Lys Arg Asn Leu
 145 150 155 160

Ala Leu Asp Glu Ala Gly Gln Arg Ser Thr Met Xaa
 165 170

<210> 478

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (61)

<223> Xaa equals stop translation

<400> 478

Met Cys Ile His Val Phe Met Xaa Val Leu Trp Val Leu Phe Leu Leu
 1 5 10 15

Asn Pro Leu Cys Thr Gly Leu Trp Pro Leu Xaa Asn Cys Phe Ser Val
 20 25 30

Leu Arg His Ala Asp Trp Val Leu Gly Ala Asp Tyr Lys Gly Glu Glu
 35 40 45

Leu Asn Arg His Gln Gly Pro Met Lys Pro Lys Asp Xaa
 50 55 60

<210> 479

<211> 3

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

303

<223> Xaa equals stop translation

<400> 479

Gly Arg Xaa

1

<210> 480

<211> 96

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (96)

<223> Xaa equals stop translation

<400> 480

Met	Phe	His	Val	Leu	Met	Ala	Gln	Val	Thr	Xaa	Val	Ile	Ile	Thr	Thr
1					5				10					15	

Val	Ser	Val	Leu	Val	Phe	Asp	Phe	Arg	Pro	Ser	Leu	Glu	Phe	Phe	Leu
			20					25					30		

Glu	Ala	Xaa	Ser	Val	Xaa	Leu	Ser	Ile	Phe	Ile	Tyr	Asn	Ala	Ser	Lys
		35					40					45			

Pro	Gln	Val	Pro	Glu	Tyr	Ala	Pro	Arg	Gln	Glu	Arg	Ile	Arg	Asp	Leu
	50					55					60				

Ser	Gly	Asn	Leu	Trp	Glu	Arg	Ser	Ser	Gly	Asp	Gly	Glu	Glu	Leu	Glu
	65					70				75				80	

Arg	Leu	Thr	Lys	Pro	Lys	Ser	Asp	Glu	Ser	Asp	Glu	Asp	Thr	Phe	Xaa
				85					90					95	

<210> 481

<211> 171

<212> PRT

304

<213> Homo sapiens

<220>

<221> SITE

<222> (159)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (171)

<223> Xaa equals stop translation

<400> 481

Met	Arg	Gly	Pro	Ala	Gln	Ala	Lys	Leu	Leu	Pro	Gly	Ser	Ala	Ile	Gln
1				5				10						15	

Ala	Leu	Val	Gly	Leu	Ala	Arg	Pro	Leu	Val	Leu	Ala	Leu	Leu	Leu	Val
	20						25					30			

Ser	Ala	Ala	Leu	Ser	Ser	Val	Val	Ser	Arg	Thr	Asp	Ser	Pro	Ser	Pro
	35					40					45				

Thr	Val	Leu	Asn	Ser	His	Ile	Ser	Thr	Pro	Asn	Val	Asn	Ala	Leu	Thr
	50					55					60				

His	Glu	Asn	Gln	Thr	Lys	Pro	Ser	Ile	Ser	Gln	Ile	Ser	Thr	Thr	Leu
65					70					75					80

Pro	Pro	Thr	Thr	Ser	Thr	Lys	Lys	Ser	Gly	Gly	Ala	Ser	Val	Val	Pro
				85					90					95	

His	Pro	Ser	Pro	Thr	Pro	Leu	Ser	Gln	Glu	Glu	Ala	Asp	Asn	Asn	Glu
			100					105					110		

Asp	Pro	Ser	Ile	Glu	Glu	Glu	Asp	Leu	Leu	Met	Leu	Asn	Ser	Ser	Pro
			115				120						125		

Ser	Thr	Ala	Lys	Asp	Thr	Leu	Asp	Asn	Gly	Asp	Tyr	Gly	Glu	Pro	Asp
	130					135					140				

Tyr	Asp	Trp	Thr	Thr	Gly	Pro	Arg	Asp	Asp	Asp	Glu	Ser	Asp	Xaa	His
145					150					155					160

Leu	Gly	Arg	Lys	Gln	Gly	Leu	His	Gly	Asn	Xaa
			165						170	

<210> 482

<211> 623

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

305

<221> SITE

<222> (575)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 482

Met	Phe	Met	Arg	Ile	Ala	Lys	Ala	Tyr	Ala	Ala	Leu	Thr	Asp	Glu	Glu	1	5	10	15
Ser	Arg	Lys	Asn	Trp	Glu	Glu	Phe	Gly	Asn	Pro	Asp	Gly	Pro	Gln	Ala	20	25	30	
Thr	Ser	Phe	Gly	Ile	Ala	Leu	Pro	Ala	Trp	Ile	Val	Asp	Gln	Lys	Asn	35	40	45	
Ser	Ile	Leu	Val	Leu	Leu	Val	Tyr	Gly	Leu	Ala	Phe	Met	Val	Ile	Leu	50	55	60	
Pro	Val	Val	Val	Gly	Ser	Trp	Trp	Tyr	Arg	Ser	Ile	Arg	Tyr	Ser	Gly	65	70	75	80
Asp	Gln	Ile	Leu	Ile	Arg	Thr	Thr	Gln	Ile	Tyr	Thr	Tyr	Phe	Val	Tyr	85	90	95	
Lys	Thr	Arg	Asn	Met	Asp	Met	Lys	Arg	Leu	Ile	Met	Val	Leu	Xaa	Gly	100	105	110	
Ala	Ser	Glu	Phe	Asp	Pro	Gln	Tyr	Asn	Lys	Asp	Ala	Thr	Ser	Arg	Pro	115	120	125	
Thr	Asp	Asn	Ile	Leu	Ile	Pro	Gln	Leu	Ile	Arg	Glu	Ile	Gly	Ser	Ile	130	135	140	
Asn	Leu	Lys	Lys	Asn	Glu	Pro	Pro	Leu	Thr	Cys	Pro	Tyr	Ser	Leu	Lys	145	150	155	160
Ala	Arg	Val	Leu	Leu	Leu	Ser	His	Leu	Ala	Arg	Met	Lys	Ile	Pro	Glu	165	170	175	
Thr	Leu	Glu	Glu	Asp	Gln	Gln	Phe	Met	Leu	Lys	Lys	Cys	Pro	Ala	Leu	180	185	190	
Leu	Gln	Glu	Met	Val	Asn	Val	Ile	Cys	Gln	Leu	Ile	Val	Met	Ala	Arg	195	200	205	
Asn	Arg	Glu	Glu	Arg	Glu	Phe	Arg	Ala	Pro	Thr	Leu	Ala	Ser	Leu	Glu	210	215	220	
Asn	Cys	Met	Lys	Leu	Ser	Gln	Met	Ala	Val	Gln	Gly	Leu	Gln	Gln	Phe	225	230	235	240
Lys	Ser	Pro	Leu	Leu	Gln	Leu	Pro	His	Ile	Glu	Glu	Asp	Asn	Leu	Arg	245	250	255	
Arg	Val	Ser	Asn	His	Lys	Lys	Tyr	Lys	Ile	Lys	Thr	Ile	Gln	Asp	Leu	260	265	270	
Val	Ser	Leu	Lys	Glu	Ser	Asp	Arg	His	Thr	Leu	Leu	His	Phe	Leu	Glu	275	280	285	

306

Asp Glu Lys Tyr Glu Glu Val Met Ala Val Leu Gly Ser Phe Pro Tyr
 290 295 300
 Val Thr Met Asp Ile Lys Ser Gln Val Leu Asp Asp Glu Asp Ser Asn
 305 310 315 320
 Asn Ile Thr Val Gly Ser Leu Val Thr Val Leu Val Lys Leu Thr Arg
 325 330 335
 Gln Thr Met Ala Glu Val Phe Glu Lys Glu Gln Ser Ile Cys Ala Ala
 340 345 350
 Glu Glu Gln Pro Ala Glu Asp Gly Gln Gly Glu Thr Asn Lys Asn Arg
 355 360 365
 Thr Lys Gly Gly Trp Gln Gln Lys Ser Lys Gly Pro Lys Lys Thr Ala
 370 375 380
 Lys Ser Lys Lys Lys Lys Pro Leu Lys Lys Lys Pro Thr Pro Val Leu
 385 390 395 400
 Leu Pro Gln Ser Lys Gln Gln Lys Gln Lys Gln Ala Asn Gly Val Val
 405 410 415
 Gly Asn Glu Ala Ala Val Lys Glu Asp Glu Glu Glu Val Ser Asp Lys
 420 425 430
 Gly Ser Asp Ser Glu Glu Glu Glu Thr Asn Arg Asp Ser Gln Ser Glu
 435 440 445
 Lys Asp Asp Gly Ser Asp Arg Asp Ser Asp Arg Glu Gln Asp Glu Lys
 450 455 460
 Gln Asn Lys Asp Asp Glu Ala Glu Trp Gln Glu Leu Gln Gln Ser Ile
 465 470 475 480
 Gln Arg Lys Glu Arg Ala Leu Leu Glu Thr Lys Ser Lys Ile Thr His
 485 490 495
 Pro Val Tyr Ser Leu Tyr Phe Pro Glu Glu Lys Gln Glu Trp Trp Trp
 500 505 510
 Leu Tyr Ile Ala Asp Arg Lys Glu Gln Thr Leu Ile Ser Met Pro Tyr
 515 520 525
 His Val Cys Thr Leu Lys Asp Thr Glu Glu Val Glu Leu Lys Phe Pro
 530 535 540
 Ala Pro Gly Lys Pro Gly Asn Tyr Gln Tyr Thr Val Phe Leu Arg Ser
 545 550 555 560
 Asp Ser Tyr Met Gly Leu Asp Gln Ile Lys Pro Leu Glu Val Xaa Lys
 565 570 575
 Phe Met Arg Leu Lys Pro Val Pro Glu Asn His Pro Gln Trp Asp Thr
 580 585 590

307

Ala Ile Glu Gly Asp Glu Asp Gln Glu Asp Ser Glu Gly Phe Glu Asp
 595 600 605

Ser Phe Glu Gly Gly Arg Gly Arg Glu Glu Gly Arg Trp Trp Thr
 610 615 620

<210> 483

<211> 92

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (29)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (92)

<223> Xaa equals stop translation

<400> 483

Met Lys Ala Ser Gln Cys Cys Cys Cys Leu Ser His Leu Leu Ala Ser
 1 5 10 15

Val Leu Leu Leu Leu Leu Leu Pro Glu Leu Ser Gly Xaa Leu Xaa Val
 20 25 30

Leu Leu Gln Ala Ala Glu Ala Ala Pro Gly Xaa Gly Pro Pro Asp Pro
 35 40 45

Arg Pro Gly His Tyr Arg Arg Cys His Arg Ala Leu Thr Pro Ala Gln
 50 55 60

Gln Pro Gly Arg Gly Leu Ala Glu Ala Ala Gly Ala Ala Gly Leu Arg
 65 70 75 80

Gly Arg Gln Trp Gln Gln Pro Cys Gly Arg Ala Xaa
 85 90

<210> 484

<211> 14

<212> PRT

<213> Homo sapiens

<220>

308

<221> SITE
<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (14)
<223> Xaa equals stop translation

<400> 484
Met Phe Lys Cys Leu Gln Thr Thr Phe Leu Phe Ile Xaa Xaa
1 5 10

<210> 485
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (54)
<223> Xaa equals stop translation

<400> 485
Ile Leu Leu Cys Ser Trp Pro Thr Gly Leu Val Gly Gly Arg Asp Pro
1 5 10 15

Gly Ser Ser Arg Gly Ser Ser Ala Ser Leu Thr Pro Ser Pro Gly Arg
20 25 30

Gln Pro Cys Ser Arg Arg Arg Gly Tyr Ser Val Gly Arg Arg Ser Ser
35 40 45

Pro Pro Asp Gly Ser Xaa
50

<210> 486
<211> 22
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (11)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

309

<220>

<221> SITE

<222> (22)

<223> Xaa equals stop translation

<400> 486

Met Ala Phe Val Leu Leu Xaa Cys Phe Val Xaa Leu Gln Ser Ser Xaa
1 5 10 15

Gly Arg Ala Val Gln Xaa
20

<210> 487

<211> 19

<212> PRT

<213> Homo sapiens

<400> 487

Glu Asn Met Ile Cys Val Lys Cys Leu Pro Gln Tyr Pro Glu His Ser
1 5 10 15

Lys His Val

<210> 488

<211> 20

<212> PRT

<213> Homo sapiens

<400> 488

Ala Arg Val Ala Phe His Leu Ile Cys Arg Tyr Ile Leu Pro Thr Val
1 5 10 15

Tyr Cys His Val
20

<210> 489

<211> 20

<212> PRT

<213> Homo sapiens

<400> 489

Glu Leu Val Glu Ser Pro Gly Ala Ala Gly Asn Ser Ala Arg Ser Gly
1 5 10 15

Asn Val Val Cys
20

<210> 490

<211> 25

<212> PRT

<213> Homo sapiens

<220>

310

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 490

Phe Lys Lys Leu Val Asn Pro Arg Xaa Gln Gly Ile Arg His Glu Glu
 1 5 10 15

Glu Ala Val Ser Trp Gln Glu Arg Arg
 20 25

<210> 491

<211> 206

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 491

Ile Ser Val Leu Xaa Tyr Pro His Cys Val Val His Glu Leu Pro Glu
 1 5 10 15

Leu Thr Ala Glu Ser Leu Glu Ala Gly Asp Ser Asn Gln Phe Cys Trp
 20 25 30

Arg Asn Leu Phe Ser Cys Ile Asn Leu Leu Arg Ile Leu Asn Lys Leu
 35 40 45

Thr Lys Trp Lys His Ser Arg Thr Met Met Leu Val Val Phe Lys Ser
 50 55 60

Ala Pro Ile Leu Lys Arg Ala Leu Lys Val Lys Gln Ala Met Met Gln
 65 70 75 80

Leu Tyr Val Leu Lys Leu Leu Lys Val Gln Thr Lys Tyr Leu Gly Arg
 85 90 95

Gln Trp Arg Lys Ser Asn Met Lys Thr Met Ser Ala Ile Tyr Gln Lys
 100 105 110

Val Arg His Arg Leu Asn Asp Asp Trp Ala Tyr Gly Asn Asp Leu Asp
 115 120 125

Ala Arg Pro Trp Asp Phe Gln Ala Glu Glu Cys Ala Leu Arg Ala Asn
 130 135 140

Ile Glu Arg Phe Asn Ala Arg Arg Tyr Asp Arg Ala His Ser Asn Pro
 145 150 155 160

Asp Phe Leu Pro Val Asp Asn Cys Leu Gln Ser Val Leu Gly Gln Arg
 165 170 175

Val Asp Leu Pro Glu Asp Phe Gln Met Asn Tyr Asp Leu Trp Leu Glu
 180 185 190

311

Arg Glu Val Phe Ser Lys Pro Ile Ser Trp Glu Glu Leu Leu
 195 200 205

<210> 492

<211> 507

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (87)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (95)

<223> Xaa equals any of the naturally occurring L-amino acids.

<400> 492

Met Arg Ala Ala Ser Pro Pro Ala Ser Ala Ser Asp Leu Ile Glu Gln
 1 5 10 15

Gln Gln Lys Arg Gly Arg Arg Glu His Lys Ala Leu Ile Lys Gln Asp
 20 25 30

Asn Leu Asp Ala Phe Asn Glu Arg Asp Pro Tyr Lys Ala Asp Asp Ser
 35 40 45

Arg Glu Glu Glu Glu Glu Asn Asp Asp Asp Asn Ser Leu Glu Gly Glu
 50 55 60

Thr Phe Pro Leu Glu Arg Asp Glu Val Met Pro Pro Pro Leu Gln His
 65 70 75 80

Pro Gln Thr Asp Arg Leu Xaa Cys Pro Lys Gly Leu Pro Trp Xaa Pro
 85 90 95

Lys Val Arg Glu Lys Asp Ile Glu Met Phe Leu Glu Ser Ser Arg Ser
 100 105 110

Lys Phe Ile Gly Tyr Thr Leu Gly Ser Asp Thr Asn Thr Val Val Gly
 115 120 125

Leu Pro Arg Pro Ile His Glu Ser Ile Lys Thr Leu Lys Gln His Lys
 130 135 140

Tyr Thr Ser Ile Ala Glu Val Gln Ala Gln Met Glu Glu Glu Tyr Leu
 145 150 155 160

Arg Ser Pro Leu Ser Gly Gly Glu Glu Glu Val Glu Gln Val Pro Ala
 165 170 175

Glu Thr Leu Tyr Gln Gly Leu Leu Pro Ser Leu Pro Gln Tyr Met Ile
 180 185 190

Ala Leu Leu Lys Ile Leu Leu Ala Ala Ala Pro Thr Ser Lys Ala Lys

312

195	200	205
Thr Asp Ser Ile Asn Ile Leu Ala Asp Val Leu Pro Glu Glu Met Pro 210 215 220		
Thr Thr Val Leu Gln Ser Met Lys Leu Gly Val Asp Val Asn Arg His 225 230 235 240		
Lys Glu Val Ile Val Lys Ala Ile Ser Ala Val Leu Leu Leu Leu Leu 245 250 255		
Lys His Phe Lys Leu Asn His Val Tyr Gln Phe Glu Tyr Met Ala Gln 260 265 270		
His Leu Val Phe Ala Asn Cys Ile Pro Leu Ile Leu Lys Phe Phe Asn 275 280 285		
Gln Asn Ile Met Ser Tyr Ile Thr Ala Lys Asn Ser Ile Ser Val Leu 290 295 300		
Asp Tyr Pro His Cys Val Val His Glu Leu Pro Glu Leu Thr Ala Glu 305 310 315 320		
Ser Leu Glu Ala Gly Asp Ser Asn Gln Phe Cys Trp Arg Asn Leu Phe 325 330 335		
Ser Cys Ile Asn Leu Leu Arg Ile Leu Asn Lys Leu Thr Lys Trp Lys 340 345 350		
His Ser Arg Thr Met Met Leu Val Val Phe Lys Ser Ala Pro Ile Leu 355 360 365		
Lys Arg Ala Leu Lys Val Lys Gln Ala Met Met Gln Leu Tyr Val Leu 370 375 380		
Lys Leu Leu Lys Val Gln Thr Lys Tyr Leu Gly Arg Gln Trp Arg Lys 385 390 395 400		
Ser Asn Met Lys Thr Met Ser Ala Ile Tyr Gln Lys Val Arg His Arg 405 410 415		
Leu Asn Asp Asp Trp Ala Tyr Gly Asn Asp Leu Asp Ala Arg Pro Trp 420 425 430		
Asp Phe Gln Ala Glu Glu Cys Ala Leu Arg Ala Asn Ile Glu Arg Phe 435 440 445		
Asn Ala Arg Arg Tyr Asp Arg Ala His Ser Asn Pro Asp Phe Leu Pro 450 455 460		
Val Asp Asn Cys Leu Gln Ser Val Leu Gly Gln Arg Val Asp Leu Pro 465 470 475 480		
Glu Asp Phe Gln Met Asn Tyr Asp Leu Trp Leu Glu Arg Glu Val Phe 485 490 495		
Ser Lys Pro Ile Ser Trp Glu Glu Leu Leu Gln 500 505		

313

<210> 493
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 493
 Met Arg Ala Ala Ser Pro Pro Ala Ser Ala Ser Asp Leu Ile Glu Gln
 1 5 10 15
 Gln Gln Lys Arg Gly Arg Arg Glu His Lys Ala Leu Ile Lys Gln Asp
 20 25 30
 Asn Leu Asp Ala Phe Asn Glu Arg Asp Pro Tyr Lys Ala Asp Asp Ser
 35 40 45
 Arg Glu
 50

<210> 494
 <211> 45
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (45)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 494
 Glu Glu Glu Glu Asn Asp Asp Asp Asn Ser Leu Glu Gly Glu Thr Phe
 1 5 10 15
 Pro Leu Glu Arg Asp Glu Val Met Pro Pro Pro Leu Gln His Pro Gln
 20 25 30
 Thr Asp Arg Leu Xaa Cys Pro Lys Gly Leu Pro Trp Xaa
 35 40 45

<210> 495
 <211> 51
 <212> PRT
 <213> Homo sapiens

<400> 495
 Pro Lys Val Arg Glu Lys Asp Ile Glu Met Phe Leu Glu Ser Ser Arg
 1 5 10 15
 Ser Lys Phe Ile Gly Tyr Thr Leu Gly Ser Asp Thr Asn Thr Val Val
 20 25 30

Gly Leu Pro Arg Pro Ile His Glu Ser Ile Lys Thr Leu Lys Gln His
35 40 45

Lys Tyr Thr
50

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<210> 496
<211> 47
<212> PRT
<213> Homo sapiens
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<400> 496
Ser Ile Ala Glu Val Gln Ala Gln Met Glu Glu Glu Tyr Leu Arg Ser
1 5 10 15

Pro Leu Ser Gly Gly Glu Glu Glu Val Glu Gln Val Pro Ala Glu Thr
20 25 30

Leu Tyr Gln Gly Leu Leu Pro Ser Leu Pro Gln Tyr Met Ile Ala
35 40 45

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<210> 497
<211> 48
<212> PRT
<213> Homo sapiens
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<400> 497
Leu Leu Lys Ile Leu Leu Ala Ala Ala Pro Thr Ser Lys Ala Lys Thr
1 5 10 15

Asp Ser Ile Asn Ile Leu Ala Asp Val Leu Pro Glu Glu Met Pro Thr
20 25 30

Thr Val Leu Gln Ser Met Lys Leu Gly Val Asp Val Asn Arg His Lys
35 40 45

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<210> 498
<211> 50
<212> PRT
<213> Homo sapiens
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<400> 498
Glu Val Ile Val Lys Ala Ile Ser Ala Val Leu Leu Leu Leu Lys
1 5 10 15

His Phe Lys Leu Asn His Val Tyr Gln Phe Glu Tyr Met Ala Gln His
20 25 30

Leu Val Phe Ala Asn Cys Ile Pro Leu Ile Leu Lys Phe Phe Asn Gln
35 40 45

315

Asn Ile
50

<210> 499
<211> 48
<212> PRT
<213> Homo sapiens

<400> 499
Met Ser Tyr Ile Thr Ala Lys Asn Ser Ile Ser Val Leu Asp Tyr Pro
1 5 10 15
His Cys Val Val His Glu Leu Pro Glu Leu Thr Ala Glu Ser Leu Glu
20 25 30
Ala Gly Asp Ser Asn Gln Phe Cys Trp Arg Asn Leu Phe Ser Cys Ile
35 40 45

<210> 500
<211> 47
<212> PRT
<213> Homo sapiens

<400> 500
Asn Leu Leu Arg Ile Leu Asn Lys Leu Thr Lys Trp Lys His Ser Arg
1 5 10 15
Thr Met Met Leu Val Val Phe Lys Ser Ala Pro Ile Leu Lys Arg Ala
20 25 30
Leu Lys Val Lys Gln Ala Met Met Gln Leu Tyr Val Leu Lys Leu
35 40 45

<210> 501
<211> 45
<212> PRT
<213> Homo sapiens

<400> 501
Leu Lys Val Gln Thr Lys Tyr Leu Gly Arg Gln Trp Arg Lys Ser Asn
1 5 10 15
Met Lys Thr Met Ser Ala Ile Tyr Gln Lys Val Arg His Arg Leu Asn
20 25 30
Asp Asp Trp Ala Tyr Gly Asn Asp Leu Asp Ala Arg Pro
35 40 45

<210> 502
<211> 48
<212> PRT

316

<213> Homo sapiens

<400> 502

Trp Asp Phe Gln Ala Glu Glu Cys Ala Leu Arg Ala Asn Ile Glu Arg
 1 5 10 15

Phe Asn Ala Arg Arg Tyr Asp Arg Ala His Ser Asn Pro Asp Phe Leu
 20 25 30

Pro Val Asp Asn Cys Leu Gln Ser Val Leu Gly Gln Arg Val Asp Leu
 35 40 45

<210> 503

<211> 28

<212> PRT

<213> Homo sapiens

<400> 503

Pro Glu Asp Phe Gln Met Asn Tyr Asp Leu Trp Leu Glu Arg Glu Val
 1 5 10 15

Phe Ser Lys Pro Ile Ser Trp Glu Glu Leu Leu Gln
 20 25

<210> 504

<211> 317

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (112)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 504

Met Ala Pro Pro Ala Pro Gly Pro Ala Ser Gly Gly Ser Gly Glu Val
 1 5 10 15

Asp Glu Leu Phe Asp Val Lys Asn Ala Phe Tyr Ile Gly Ser Tyr Gln
 20 25 30

Gln Cys Ile Asn Glu Ala Xaa Xaa Val Lys Leu Ser Ser Pro Glu Arg
 35 40 45

317

Asp Val Glu Arg Asp Val Phe Leu Tyr Arg Ala Tyr Leu Ala Gln Arg
 50 55 60
 Lys Phe Gly Val Val Leu Asp Glu Ile Lys Pro Ser Ser Ala Pro Glu
 65 70 75 80
 Leu Gln Ala Val Arg Met Phe Ala Asp Tyr Leu Ala His Glu Ser Arg
 85 90 95
 Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg Ser Xaa
 100 105 110
 Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile Tyr Leu
 115 120 125
 His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln Gly Asp
 130 135 140
 Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys Leu Asp
 145 150 155 160
 Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp Leu Asp
 165 170 175
 Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val Ser Leu Ala
 180 185 190
 Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe Gln Glu Met
 195 200 205
 Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly Gln Ala Ala
 210 215 220
 Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu Gly Leu Leu Gln
 225 230 235 240
 Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr Leu Val Asn Leu
 245 250 255
 Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu Val Thr Asn Arg
 260 265 270
 Tyr Leu Ser Gln Leu Lys Asp Ala His Arg Ser His Pro Phe Ile Lys
 275 280 285
 Glu Tyr Gln Ala Lys Glu Asn Asp Phe Asp Arg Leu Val Leu Gln Tyr
 290 295 300
 Ala Pro Ser Ala Glu Ala Gly Pro Glu Leu Ser Gly Pro
 305 310 315

<210> 505

<211> 261

<212> PRT

<213> Homo sapiens

<222> (65)

<400> 505

Tyr Ala Pro Ser Ala
260

319

<210> 506
 <211> 48
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (39)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (40)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 506
 Met Ala Pro Pro Ala Pro Gly Pro Ala Ser Gly Gly Ser Gly Glu Val
 1 5 10 15
 Asp Glu Leu Phe Asp Val Lys Asn Ala Phe Tyr Ile Gly Ser Tyr Gln
 20 25 30
 Gln Cys Ile Asn Glu Ala Xaa Xaa Val Lys Leu Ser Ser Pro Glu Arg
 35 40 45

<210> 507
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 507
 Asp Val Glu Arg Asp Val Phe Leu Tyr Arg Ala Tyr Leu Ala Gln Arg
 1 5 10 15
 Lys Phe Gly Val Val Leu Asp Glu Ile Lys Pro Ser Ser Ala Pro Glu
 20 25 30
 Leu Gln Ala Val Arg Met Phe Ala Asp Tyr Leu Ala His Glu Ser
 35 40 45

<210> 508
 <211> 48
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 508
 Arg Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg Ser
 1 5 10 15

320

Xaa Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile Tyr
 20 25 30
 Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln Gly
 35 40 45

<210> 509
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 509
 Asp Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys Leu
 1 5 10 15
 Asp Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp Leu
 20 25 30
 Asp Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val Ser
 35 40 45

<210> 510
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 510
 Leu Ala Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe Gln
 1 5 10 15
 Glu Met Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly Gln
 20 25 30
 Ala Ala Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu Gly
 35 40 45

<210> 511
 <211> 48
 <212> PRT
 <213> Homo sapiens

<400> 511
 Leu Leu Gln Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr Leu
 1 5 10 15
 Val Asn Leu Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu Val
 20 25 30
 Thr Asn Arg Tyr Leu Ser Gln Leu Lys Asp Ala His Arg Ser His Pro
 35 40 45

321

<210> 512
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 512
 Phe Ile Lys Glu Tyr Gln Ala Lys Glu Asn Asp Phe Asp Arg Leu Val
 1 5 10 15
 Leu Gln Tyr Ala Pro Ser Ala Glu Ala Gly Pro Glu Leu Ser Gly Pro
 20 25 30

<210> 513
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 513
 Arg Asp Val Glu Arg Asp Val Phe Leu Tyr Arg Ala Tyr Leu Ala Gln
 1 5 10 15
 Arg Lys Phe Gly Val Val Leu Asp Glu Ile Lys Pro Ser Ser Ala Pro
 20 25 30
 Glu Leu Gln Ala Val Arg Met Phe Ala Asp Tyr Leu Ala His Glu
 35 40 45

<210> 514
 <211> 48
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (18)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 514
 Ser Arg Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg
 1 5 10 15
 Ser Xaa Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile
 20 25 30
 Tyr Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln
 35 40 45

322

<210> 515
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 515
 Gly Asp Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys
 1 5 10 15
 Leu Asp Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp
 20 25 30
 Leu Asp Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val
 35 40 45

<210> 516
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 516
 Ser Leu Ala Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe
 1 5 10 15
 Gln Glu Met Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly
 20 25 30
 Gln Ala Ala Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu
 35 40 45

<210> 517
 <211> 38
 <212> PRT
 <213> Homo sapiens

<400> 517
 Gly Leu Leu Gln Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr
 1 5 10 15
 Leu Val Asn Leu Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu
 20 25 30
 Val Thr Asn Arg Tyr Leu
 35

<210> 518
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 518
 Ser Gln Leu Lys Asp Ala His Arg Ser His Pro Phe Ile Lys Glu Tyr
 1 5 10 15

323

Gln Ala Lys Glu Asn Asp Phe Asp Arg Leu Val Leu Gln Tyr Ala Pro
 20 25 30

Ser Ala

<210> 519

<211> 62

<212> PRT

<213> Homo sapiens

<400> 519

Asn Arg Tyr Tyr Arg Glu Ser Trp Ser Leu Gln Val Pro Val Arg Asn
 1 5 10 15

Ser Gly Ser Thr His Ala Ser Glu Arg Asn Gly Ala Ser Gly Pro Arg
 20 25 30

Pro Gly Leu Arg Arg Leu Arg Gly Gly Arg Arg Ala Val Arg Arg Lys
 35 40 45

Glu Arg Leu Leu His Arg Gln Leu Pro Ala Val His Lys Arg
 50 55 60

<210> 520

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 520

Ala Pro Gly Xaa Gly Trp Arg Gly Ser Leu Gly Glu Pro Pro Pro Pro
 1 5 10 15

Pro Arg Ala Ser Leu Ser Ser Asp Thr Ser Ala Leu Ser Tyr Asp Ser
 20 25 30

Val Lys Tyr Thr Leu Val Val Asp Glu His Ala Gln Leu Glu Leu Val
 35 40 45

Ser Leu Arg Arg Ala Ser Glu Thr Thr Val Thr Arg Val Thr Leu Pro
 50 55 60

Pro Ser

65

<210> 521

<211> 30

<212> PRT

<213> Homo sapiens

324

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 521

Ala Pro Gly Xaa Gly Trp Arg Gly Ser Leu Gly Glu Pro Pro Pro Pro
 1 5 10 15

Pro Arg Ala Ser Leu Ser Ser Asp Thr Ser Ala Leu Ser Tyr
 20 25 30

<210> 522

<211> 36

<212> PRT

<213> Homo sapiens

<400> 522

Asp Ser Val Lys Tyr Thr Leu Val Val Asp Glu His Ala Gln Leu Glu
 1 5 10 15

Leu Val Ser Leu Arg Arg Ala Ser Glu Thr Thr Val Thr Arg Val Thr
 20 25 30

Leu Pro Pro Ser
 35

<210> 523

<211> 156

<212> PRT

<213> Homo sapiens

<400> 523

Met Lys Ala Ile Gly Ile Glu Pro Ser Leu Ala Thr Tyr His His Ile
 1 5 10 15

Ile Arg Leu Phe Asp Gln Pro Gly Asp Pro Leu Lys Arg Ser Ser Phe
 20 25 30

Ile Ile Tyr Asp Ile Met Asn Glu Leu Met Gly Lys Arg Phe Ser Pro
 35 40 45

Lys Asp Pro Asp Asp Asp Lys Phe Phe Gln Ser Ala Met Ser Ile Cys
 50 55 60

Ser Ser Leu Arg Asp Leu Glu Leu Ala Tyr Gln Val His Gly Leu Leu
 65 70 75 80

Lys Thr Gly Asp Asn Trp Lys Phe Ile Gly Pro Asp Gln His Arg Asn
 85 90 95

Phe Tyr Tyr Ser Lys Phe Phe Asp Leu Ile Cys Leu Met Glu Gln Ile
 100 105 110

Asp Val Thr Leu Lys Trp Tyr Glu Asp Leu Ile Pro Ser Ala Tyr Phe

325

115	120	125
Pro His Ser Gln Thr Met Ile His Leu Leu Gln Ala Leu Asp Val Ala		
130	135	140
Asn Arg Leu Glu Val Ile Pro Lys Ile Trp Glu Arg		
145	150	155
<210> 524		
<211> 176		
<212> PRT		
<213> Homo sapiens		
<400> 524		
Lys Asp Ser Lys Glu Tyr Gly His Thr Phe Arg Ser Asp Leu Arg Glu		
1	5	10 15
Glu Ile Leu Met Leu Met Ala Arg Asp Lys His Pro Pro Glu Leu Gln		
20	25	30
Val Ala Phe Ala Asp Cys Ala Ala Asp Ile Lys Ser Ala Tyr Glu Ser		
35	40	45
Gln Pro Ile Arg Gln Thr Ala Gln Asp Trp Pro Ala Thr Ser Leu Asn		
50	55	60
Cys Ile Ala Ile Leu Phe Leu Arg Ala Gly Arg Thr Gln Glu Ala Trp		
65	70	75 80
Lys Met Leu Gly Leu Phe Arg Lys His Asn Lys Ile Pro Arg Ser Glu		
85	90	95
Leu Leu Asn Glu Leu Met Asp Ser Ala Lys Val Ser Asn Ser Pro Ser		
100	105	110
Gln Ala Ile Glu Val Val Glu Leu Ala Ser Ala Phe Ser Leu Pro Ile		
115	120	125
Cys Glu Gly Leu Thr Gln Arg Val Met Ser Asp Phe Ala Ile Asn Gln		
130	135	140
Glu Gln Lys Glu Ala Leu Ser Asn Leu Thr Ala Leu Thr Ser Asp Ser		
145	150	155 160
Asp Thr Asp Ser Ser Ser Asp Ser Asp Ser Asp Thr Ser Glu Gly Lys		
165	170	175

<210> 525
 <211> 49
 <212> PRT
 <213> Homo sapiens
 <400> 525

326

Met Lys Ala Ile Gly Ile Glu Pro Ser Leu Ala Thr Tyr His His Ile
 1 5 10 15
 Ile Arg Leu Phe Asp Gln Pro Gly Asp Pro Leu Lys Arg Ser Ser Phe
 20 25 30
 Ile Ile Tyr Asp Ile Met Asn Glu Leu Met Gly Lys Arg Phe Ser Pro
 35 40 45

Lys

<210> 526
 <211> 49
 <212> PRT
 <213> Homo sapiens

<400> 526
 Asp Pro Asp Asp Asp Lys Phe Phe Gln Ser Ala Met Ser Ile Cys Ser
 1 5 10 15
 Ser Leu Arg Asp Leu Glu Leu Ala Tyr Gln Val His Gly Leu Leu Lys
 20 25 30
 Thr Gly Asp Asn Trp Lys Phe Ile Gly Pro Asp Gln His Arg Asn Phe
 35 40 45

Tyr

<210> 527
 <211> 28
 <212> PRT
 <213> Homo sapiens

<400> 527
 Tyr Ser Lys Phe Phe Asp Leu Ile Cys Leu Met Glu Gln Ile Asp Val
 1 5 10 15
 Thr Leu Lys Trp Tyr Glu Asp Leu Ile Pro Ser Ala
 20 25

<210> 528
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 528
 Tyr Phe Pro His Ser Gln Thr Met Ile His Leu Leu Gln Ala Leu Asp
 1 5 10 15
 Val Ala Asn Arg Leu Glu Val Ile Pro Lys Ile Trp Glu Arg
 20 25 30

327

<210> 529

<211> 46

<212> PRT

<213> Homo sapiens

<400> 529

Lys Asp Ser Lys Glu Tyr Gly His Thr Phe Arg Ser Asp Leu Arg Glu
1 5 10 15

Glu Ile Leu Met Leu Met Ala Arg Asp Lys His Pro Pro Glu Leu Gln
20 25 30

Val Ala Phe Ala Asp Cys Ala Ala Asp Ile Lys Ser Ala Tyr
35 40 45

<210> 530

<211> 50

<212> PRT

<213> Homo sapiens

<400> 530

Glu Ser Gln Pro Ile Arg Gln Thr Ala Gln Asp Trp Pro Ala Thr Ser
1 5 10 15

Leu Asn Cys Ile Ala Ile Leu Phe Leu Arg Ala Gly Arg Thr Gln Glu
20 25 30

Ala Trp Lys Met Leu Gly Leu Phe Arg Lys His Asn Lys Ile Pro Arg
35 40 45

Ser Glu
50

<210> 531

<211> 47

<212> PRT

<213> Homo sapiens

<400> 531

Leu Leu Asn Glu Leu Met Asp Ser Ala Lys Val Ser Asn Ser Pro Ser
1 5 10 15

Gln Ala Ile Glu Val Val Glu Leu Ala Ser Ala Phe Ser Leu Pro Ile
20 25 30

Cys Glu Gly Leu Thr Gln Arg Val Met Ser Asp Phe Ala Ile Asn
35 40 45

<210> 532

<211> 33

<212> PRT

<213> Homo sapiens

<400> 532

Gln Glu Gln Lys Glu Ala Leu Ser Asn Leu Thr Ala Leu Thr Ser Asp

1 5 10 15

Ser Asp Thr Asp Ser Ser Ser Asp Ser Asp Ser Asp Thr Ser Glu Gly
20 25 30

Lys

<210> 533
<211> 324
<212> PRT
<213> Homo sapiens

<400> 533

Met Ser Ser Asp Asn Glu Ser Asp Ile Glu Asp Glu Asp Leu Lys Leu
1 5 10 15

Glu Leu Arg Arg Leu Arg Asp Lys His Leu Lys Glu Ile Gln Asp Leu
20 25 30

Gln Ser Arg Gln Lys His Glu Ile Glu Ser Leu Tyr Thr Lys Leu Gly
35 40 45

Lys Val Pro Pro Ala Val Ile Ile Pro Pro Ala Ala Pro Leu Ser Gly
50 55 60

Arg Arg Arg Arg Pro Thr Lys Ser Lys Gly Ser Lys Ser Ser Arg Ser
65 70 75 80

Ser Ser Leu Gly Asn Lys Ser Pro Gln Leu Ser Gly Asn Leu Ser Gly
85 90 95

Gln Ser Ala Ala Ser Val Leu His Pro Gln Gln Thr Leu His Pro Pro
100 105 110

Gly Asn Ile Pro Glu Ser Gly Gln Asn Gln Leu Leu Gln Pro Leu Lys
115 120 125

Pro Ser Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe Thr Ser Asp Gly
130 135 140

Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly Gln Gly Thr Ser Ser
145 150 155 160

Thr Asn Thr Val Gly Ala Thr Val Asn Ser Gln Ala Ala Gln Ala Gln
165 170 175

Pro Pro Ala Met Thr Ser Ser Arg Lys Gly Thr Phe Thr Asp Asp Leu
180 185 190

His Lys Leu Val Asp Asn Trp Ala Arg Asp Ala Met Asn Leu Ser Gly
195 200 205

Arg Arg Gly Ser Lys Gly His Met Asn Tyr Glu Gly Pro Gly Met Ala
210 215 220

Arg Lys Phe Ser Ala Pro Gly Gln Leu Cys Ile Ser Met Thr Ser Asn

329

225 230 235 240
 Leu Gly Gly Ser Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser Leu Gly
 245 250 255
 His Phe Thr Lys Ser Met Cys Pro Pro Gln Gln Tyr Gly Phe Pro Ala
 260 265 270
 Thr Pro Phe Gly Ala Gln Trp Ser Gly Thr Gly Gly Pro Ala Pro Gln
 275 280 285
 Pro Leu Gly Gln Phe Gln Pro Val Gly Thr Ala Ser Leu Gln Asn Phe
 290 295 300
 Asn Ile Ser Asn Leu Gln Lys Ser Ile Ser Asn Pro Pro Gly Ser Asn
 305 310 315 320
 Leu Arg Thr Thr

<210> 534
 <211> 133
 <212> PRT
 <213> Homo sapiens

<400> 534
 Ile Gln Asp Leu Gln Ser Arg Gln Lys His Glu Ile Glu Ser Leu Tyr
 1 5 10 15
 Thr Lys Leu Gly Lys Val Pro Pro Ala Val Ile Ile Pro Pro Ala Ala
 20 25 30
 Pro Leu Ser Gly Arg Arg Arg Arg Pro Thr Lys Ser Lys Gly Ser Lys
 35 40 45
 Ser Ser Arg Ser Ser Ser Leu Gly Asn Lys Ser Pro Gln Leu Ser Gly
 50 55 60
 Asn Leu Ser Gly Gln Ser Ala Ala Ser Val Leu His Pro Gln Gln Thr
 65 70 75 80
 Leu His Pro Pro Gly Asn Ile Pro Glu Ser Gly Gln Asn Gln Leu Leu
 85 90 95
 Gln Pro Leu Lys Pro Ser Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe
 100 105 110
 Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly Gln
 115 120 125
 Gly Thr Ser Ser Thr
 130

<210> 535
 <211> 53
 <212> PRT

330

<213> Homo sapiens

<400> 535

Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly Gln
 1 5 10 15

Gly Thr Ser Ser Thr Asn Thr Val Gly Ala Thr Val Asn Ser Gln Ala
 20 25 30

Ala Gln Ala Gln Pro Pro Ala Met Thr Ser Ser Arg Lys Gly Thr Phe
 35 40 45

Thr Asp Asp Leu His
 50

<210> 536

<211> 48

<212> PRT

<213> Homo sapiens

<400> 536

Lys Gly His Met Asn Tyr Glu Gly Pro Gly Met Ala Arg Lys Phe Ser
 1 5 10 15

Ala Pro Gly Gln Leu Cys Ile Ser Met Thr Ser Asn Leu Gly Gly Ser
 20 25 30

Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser Leu Gly His Phe Thr Lys
 35 40 45

<210> 537

<211> 31

<212> PRT

<213> Homo sapiens

<400> 537

Gln Pro Leu Lys Pro Ser Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe
 1 5 10 15

Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly
 20 25 30

<210> 538

<211> 51

<212> PRT

<213> Homo sapiens

<400> 538

Met Ser Ser Asp Asn Glu Ser Asp Ile Glu Asp Glu Asp Leu Lys Leu
 1 5 10 15

Glu Leu Arg Arg Leu Arg Asp Lys His Leu Lys Glu Ile Gln Asp Leu

331

20 25 30
 Gln Ser Arg Gln Lys His Glu Ile Glu Ser Leu Tyr Thr Lys Leu Gly
 35 40 45

Lys Val Pro
 50

<210> 539
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 539
 Pro Ala Val Ile Ile Pro Pro Ala Ala Pro Leu Ser Gly Arg Arg Arg
 1 5 10 15

Arg Pro Thr Lys Ser Lys Gly Ser Lys Ser Ser Arg Ser Ser Ser Leu
 20 25 30

Gly Asn Lys Ser Pro Gln Leu Ser Gly Asn Leu Ser Gly Gln Ser
 35 40 45

<210> 540
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 540
 Ala Ala Ser Val Leu His Pro Gln Gln Thr Leu His Pro Pro Gly Asn
 1 5 10 15

Ile Pro Glu Ser Gly Gln Asn Gln Leu Leu Gln Pro Leu Lys Pro Ser
 20 25 30

Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe Thr Ser Asp Gly Ala Ile
 35 40 45

Ser Val
 50

<210> 541
 <211> 44
 <212> PRT
 <213> Homo sapiens

<400> 541
 Pro Ser Leu Ser Ala Pro Gly Gln Gly Thr Ser Ser Thr Asn Thr Val
 1 5 10 15

Gly Ala Thr Val Asn Ser Gln Ala Ala Gln Ala Gln Pro Pro Ala Met
 20 25 30

Thr Ser Ser Arg Lys Gly Thr Phe Thr Asp Asp Leu
 35 40

332

<210> 542
<211> 46
<212> PRT
<213> Homo sapiens

<400> 542
His Lys Leu Val Asp Asn Trp Ala Arg Asp Ala Met Asn Leu Ser Gly
1 5 10 15
Arg Arg Gly Ser Lys Gly His Met Asn Tyr Glu Gly Pro Gly Met Ala
20 25 30
Arg Lys Phe Ser Ala Pro Gly Gln Leu Cys Ile Ser Met Thr
35 40 45

<210> 543
<211> 46
<212> PRT
<213> Homo sapiens

<400> 543
Ser Asn Leu Gly Gly Ser Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser
1 5 10 15
Leu Gly His Phe Thr Lys Ser Met Cys Pro Pro Gln Gln Tyr Gly Phe
20 25 30
Pro Ala Thr Pro Phe Gly Ala Gln Trp Ser Gly Thr Gly Gly
35 40 45

<210> 544
<211> 40
<212> PRT
<213> Homo sapiens

<400> 544
Pro Ala Pro Gln Pro Leu Gly Gln Phe Gln Pro Val Gly Thr Ala Ser
1 5 10 15
Leu Gln Asn Phe Asn Ile Ser Asn Leu Gln Lys Ser Ile Ser Asn Pro
20 25 30
Pro Gly Ser Asn Leu Arg Thr Thr
35 40

<210> 545
<211> 57
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (10)

333

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 545

Val Arg Val Ala Ala Ala Glu Ser Met Xaa Leu Leu Leu Glu Cys Ala
1 5 10 15

Xaa Val Arg Gly Pro Glu Tyr Leu Thr Gln Met Trp His Phe Met Cys
20 25 30

Asp Ala Leu Ile Lys Ala Ile Gly Thr Glu Pro Asp Ser Asp Val Leu
35 40 45

Ser Glu Ile Met His Ser Phe Ala Lys
50 55

<210> 546

<211> 85

<212> PRT

<213> Homo sapiens

<400> 546

Met Glu Ile Asn Asn Gln Asn Cys Phe Ile Val Ile Asp Leu Val Arg
1 5 10 15

Thr Val Met Glu Asn Gly Val Glu Gly Leu Leu Ile Phe Gly Ala Phe
20 25 30

Leu Pro Glu Ser Trp Leu Ile Gly Val Arg Cys Ser Ser Glu Pro Pro
35 40 45

Lys Ala Leu Leu Leu Ile Leu Ala His Ser Gln Lys Arg Arg Leu Asp
50 55 60

Gly Trp Ser Phe Ile Arg His Leu Arg Val His Tyr Cys Val Ser Leu
65 70 75 80

Thr Ile His Phe Ser
85

<210> 547

<211> 100

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

334

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 547

Gly	Gly	Arg	Glu	Ala	Asn	Lys	Xaa	Phe	Phe	Ile	Glu	Ser	Cys	Ile	Ala
1				5				10						15	

Leu	Phe	Val	Ser	Phe	Ile	Ile	Asn	Val	Phe	Val	Val	Ser	Val	Phe	Ala
		20					25						30		

Glu	Xaa	Phe	Phe	Gly	Xaa	Thr	Asn	Glu	Gln	Val	Val	Glu	Val	Cys	Thr
	35					40						45			

Asn	Thr	Ser	Ser	Pro	His	Ala	Gly	Leu	Phe	Pro	Lys	Asp	Asn	Ser	Thr
	50					55					60				

Leu	Ala	Val	Asp	Ile	Tyr	Lys	Gly	Gly	Val	Val	Leu	Gly	Cys	Tyr	Phe
65					70					75					80

Gly	Pro	Ala	Ala	Leu	Tyr	Ile	Trp	Ala	Val	Gly	Ile	Leu	Ala	Ala	Gly
				85					90						95

Gln	Ser	Ser	Thr
			100

<210> 548

<211> 45

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 548

Gly	Gly	Arg	Glu	Ala	Asn	Lys	Xaa	Phe	Phe	Ile	Glu	Ser	Cys	Ile	Ala
1				5				10						15	

Leu	Phe	Val	Ser	Phe	Ile	Ile	Asn	Val	Phe	Val	Val	Ser	Val	Phe	Ala
		20					25						30		

335

Glu Xaa Phe Phe Gly Xaa Thr Asn Glu Gln Val Val Glu
35 40 45

<210> 549
<211> 55
<212> PRT
<213> Homo sapiens

<400> 549
Val Cys Thr Asn Thr Ser Ser Pro His Ala Gly Leu Phe Pro Lys Asp
1 5 10 15

Asn Ser Thr Leu Ala Val Asp Ile Tyr Lys Gly Gly Val Val Leu Gly
20 25 30

Cys Tyr Phe Gly Pro Ala Ala Leu Tyr Ile Trp Ala Val Gly Ile Leu
35 40 45

Ala Ala Gly Gln Ser Ser Thr
50 55

<210> 550
<211> 20
<212> PRT
<213> Homo sapiens

<400> 550
Gln Asp Lys His Ala Glu Glu Val Arg Lys Asn Lys Glu Leu Lys Glu
1 5 10 15

Glu Ala Ser Arg
20

<210> 551
<211> 92
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (20)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

336

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 551

Gln	Gln	Asp	Leu	Ser	Pro	Trp	Ala	Ala	Pro	Val	Gly	Cys	Pro	Leu	Xaa
1				5					10					15	

Xaa	Ala	Ser	Xaa	Thr	Cys	His	Xaa	Leu	Pro	Leu	Ser	Gly	Cys	Leu	Arg
		20						25					30		

Arg	Gln	Ser	Xaa	Ser	Leu	Pro	Val	Val	Ala	Xaa	Leu	Cys	Phe	Trp	Phe
		35					40					45			

Ser	Cys	Pro	Leu	Ala	Ser	Leu	Phe	Val	Pro	Gly	Gln	Pro	Cys	Val	Thr
	50					55					60				

Cys	Pro	Phe	Pro	Ser	Leu	Pro	Phe	Gln	Asp	Lys	His	Ala	Glu	Glu	Val
65					70					75				80	

Arg	Lys	Asn	Lys	Glu	Leu	Lys	Glu	Glu	Ala	Ser	Arg
			85							90	

<210> 552

<211> 37

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 552

Pro	Thr	Arg	Cys	Cys	Thr	Thr	Gln	Pro	Cys	Arg	Ser	Ser	Ala	Arg	Arg
1				5					10					15	

Pro	Cys	Trp	Val	Pro	Met	Val	Pro	Ser	Pro	Glu	Gly	Arg	Glu	Xaa	Gln
		20						25					30		

Pro	Thr	Cys	Pro	Ser
				35

<210> 553

<211> 363

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (211)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 553

Met	Lys	Arg	Ser	Leu	Asn	Glu	Asn	Ser	Ala	Arg	Ser	Thr	Ala	Gly	Cys
1				5					10					15	

Leu	Pro	Val	Pro	Leu	Phe	Asn	Gln	Lys	Lys	Arg	Asn	Arg	Gln	Pro	Leu
			20					25					30		

Thr	Ser	Asn	Pro	Leu	Lys	Asp	Asp	Ser	Gly	Ile	Ser	Thr	Pro	Ser	Asp
		35					40					45			

Asn	Tyr	Asp	Phe	Pro	Pro	Leu	Pro	Thr	Asp	Trp	Ala	Trp	Glu	Ala	Val
	50					55					60				

Asn	Pro	Glu	Xaa	Ala	Pro	Val	Met	Lys	Thr	Val	Asp	Thr	Gly	Gln	Ile
65					70					75					80

Pro	His	Ser	Val	Ser	Arg	Pro	Leu	Arg	Ser	Gln	Asp	Ser	Val	Phe	Asn
				85					90					95	

Ser	Ile	Gln	Ser	Asn	Thr	Gly	Arg	Ser	Gln	Gly	Gly	Trp	Ser	Tyr	Arg
		100						105					110		

Asp	Gly	Asn	Lys	Asn	Thr	Ser	Leu	Lys	Thr	Trp	Xaa	Lys	Asn	Asp	Phe
	115						120					125			

Lys	Pro	Gln	Cys	Lys	Arg	Thr	Asn	Leu	Val	Ala	Asn	Asp	Gly	Lys	Asn
	130					135					140				

Ser	Cys	Pro	Met	Ser	Ser	Gly	Ala	Gln	Gln	Gln	Lys	Gln	Leu	Arg	Thr
145					150					155					160

Pro	Glu	Pro	Pro	Asn	Leu	Ser	Arg	Asn	Lys	Glu	Thr	Glu	Leu	Leu	Arg
				165					170					175	

Gln	Thr	His	Ser	Ser	Lys	Ile	Ser	Gly	Cys	Thr	Met	Arg	Gly	Leu	Asp
			180					185					190		

Lys	Asn	Ser	Ala	Leu	Gln	Thr	Leu	Lys	Pro	Asn	Phe	Gln	Gln	Asn	Gln
	195						200					205			

Tyr	Lys	Xaa	Gln	Met	Leu	Asp	Asp	Ile	Pro	Glu	Asp	Asn	Thr	Leu	Lys
	210					215					220				

338

Glu Thr Ser Leu Tyr Gln Leu Gln Phe Lys Glu Lys Ala Ser Ser Leu
225 230 235 240

Arg Ile Ile Ser Ala Val Ile Glu Ser Met Lys Tyr Trp Arg Glu His
245 250 255

Ala Gln Lys Thr Val Leu Leu Phe Glu Val Leu Ala Val Leu Asp Ser
260 265 270

Ala Val Thr Pro Gly Pro Tyr Tyr Ser Lys Thr Phe Leu Met Arg Asp
275 280 285

Gly Lys Asn Thr Leu Pro Cys Val Phe Tyr Glu Ile Asp Arg Glu Leu
290 295 300

Pro Arg Leu Ile Arg Gly Arg Val His Arg Cys Val Gly Asn Tyr Asp
305 310 315 320

Gln Lys Lys Asn Ile Phe Gln Cys Val Ser Val Arg Pro Ala Ser Val
325 330 335

Ser Glu Gln Lys Thr Phe Gln Ala Phe Val Lys Ile Ala Asp Val Glu
340 345 350

Met Gln Tyr Tyr Ile Asn Val Met Asn Glu Thr
355 360

<210> 554

<211> 45

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 554

Ser Gln Asp Ser Val Phe Asn Ser Ile Gln Ser Asn Thr Gly Arg Ser
1 5 10 15

Gln Gly Gly Trp Ser Tyr Arg Asp Gly Asn Lys Asn Thr Ser Leu Lys
20 25 30

Thr Trp Xaa Lys Asn Asp Phe Lys Pro Gln Cys Lys Arg
35 40 45

<210> 555

<211> 36

<212> PRT

<213> Homo sapiens

<400> 555

Asn Lys Glu Thr Glu Leu Leu Arg Gln Thr His Ser Ser Lys Ile Ser
1 5 10 15

339

Gly Cys Thr Met Arg Gly Leu Asp Lys Asn Ser Ala Leu Gln Thr Leu
 20 25 30

Lys Pro Asn Phe
 35

<210> 556
 <211> 49
 <212> PRT
 <213> Homo sapiens

<400> 556
 Ser Ser Leu Arg Ile Ile Ser Ala Val Ile Glu Ser Met Lys Tyr Trp
 1 5 10 15

Arg Glu His Ala Gln Lys Thr Val Leu Leu Phe Glu Val Leu Ala Val
 20 25 30

Leu Asp Ser Ala Val Thr Pro Gly Pro Tyr Tyr Ser Lys Thr Phe Leu
 35 40 45

Met

<210> 557
 <211> 42
 <212> PRT
 <213> Homo sapiens

<400> 557
 Pro Arg Leu Ile Arg Gly Arg Val His Arg Cys Val Gly Asn Tyr Asp
 1 5 10 15

Gln Lys Lys Asn Ile Phe Gln Cys Val Ser Val Arg Pro Ala Ser Val
 20 25 30

Ser Glu Gln Lys Thr Phe Gln Ala Phe Val
 35 40

<210> 558
 <211> 370
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (320)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (334)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (337)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (339)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (341)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (345)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (350)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (352)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (355)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (360)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 558
 Gly Val Phe Arg Pro Cys Val Cys Gly Arg Pro Ala Ser Leu Thr Cys
 1 5 10 15
 Ser Pro Leu Asp Pro Glu Val Gly Pro Tyr Cys Asp Thr Pro Thr Met
 20 25 30
 Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro Val
 35 40 45
 His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys Thr
 50 55 60
 Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg Gly
 65 70 75 80
 Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His Arg
 85 90 95

341

Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp Val
 100 105 110
 Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr Lys
 115 120 125
 Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln Leu
 130 135 140
 Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp Val
 145 150 155 160
 Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu His
 165 170 175
 Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe Arg
 180 185 190
 Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr Val
 195 200 205
 Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu Val
 210 215 220
 Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met Leu
 225 230 235 240
 Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu Leu
 245 250 255
 Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met Phe
 260 265 270
 Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe Ser
 275 280 285
 Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn Ala
 290 295 300
 Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys Xaa
 305 310 315 320
 Lys Trp Arg Thr Lys Ser Ser Trp Gly Ser Thr Ser Met Xaa Trp Thr
 325 330 335
 Xaa Arg Xaa Pro Xaa Asp Ala Arg Xaa Pro Val Val Gly Xaa Arg Xaa
 340 345 350
 Ile Gln Xaa Leu Lys Asp His Xaa Pro Arg Met Val Leu Asp Ser Lys
 355 360 365
 Pro Gln
 370

<210> 559

<211> 39

342

<212> PRT

<213> Homo sapiens

<400> 559

Thr Cys Ser Pro Leu Asp Pro Glu Val Gly Pro Tyr Cys Asp Thr Pro
 1 5 10 15

Thr Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser
 20 25 30

Pro Val His Thr Thr Leu Ser
 35

<210> 560

<211> 54

<212> PRT

<213> Homo sapiens

<400> 560

Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His Arg
 1 5 10 15

Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp Val
 20 25 30

Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr Lys
 35 40 45

Val Phe Gly Ser Lys Phe
 50

<210> 561

<211> 52

<212> PRT

<213> Homo sapiens

<400> 561

Arg Glu Met Phe Glu Val Thr Gly Leu His Asp Val Asp Gln Gly Trp
 1 5 10 15

Met Arg Ala Val Arg Lys His Ala Lys Gly Leu His Ile Val Pro Arg
 20 25 30

Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe Arg Asn Val Leu Asp
 35 40 45

Ser Glu Asp Glu
 50

<210> 562

<211> 56

<212> PRT

<213> Homo sapiens

<400> 562

343

His Phe Asp Gly Phe Val Val Glu Val Trp Asn Gln Leu Leu Ser Gln
 1 5 10 15
 Lys Arg Val Gly Leu Ile His Met Leu Thr His Leu Ala Glu Ala Leu
 20 25 30
 His Gln Ala Arg Leu Leu Ala Leu Val Ile Pro Pro Ala Ile Thr
 35 40 45
 Pro Gly Thr Asp Gln Leu Gly Met
 50 55

<210> 563

<211> 47

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 563

Asp Gly Phe Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro
 1 5 10 15
 Gly Pro Asn Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu
 20 25 30
 Asp Pro Lys Xaa Lys Trp Arg Thr Lys Ser Ser Trp Gly Ser Thr
 35 40 45

<210> 564

<211> 152

<212> PRT

<213> Homo sapiens

<400> 564

Glu Arg Gly Val Ser Ile Asn Gln Phe Cys Lys Glu Phe Asn Glu Arg
 1 5 10 15
 Thr Lys Asp Ile Lys Glu Gly Ile Pro Leu Pro Thr Lys Ile Leu Val
 20 25 30
 Lys Pro Asp Arg Thr Phe Glu Ile Lys Ile Gly Gln Pro Thr Val Ser
 35 40 45
 Tyr Phe Leu Lys Ala Ala Ala Gly Ile Glu Lys Gly Ala Arg Gln Thr
 50 55 60
 Gly Lys Glu Val Ala Gly Leu Val Thr Leu Lys His Val Tyr Glu Ile
 65 70 75 80
 Ala Arg Ile Lys Ala Gln Asp Glu Ala Phe Ala Leu Gln Asp Val Pro
 85 90 95

344

Leu Ser Ser Val Val Arg Ser Ile Ile Gly Ser Ala Arg Ser Leu Gly
 100 105 110
 Ile Arg Val Val Lys Asp Leu Ser Ser Glu Glu Leu Ala Ala Phe Gln
 115 120 125
 Lys Glu Arg Ala Ile Phe Leu Ala Ala Gln Lys Glu Ala Asp Leu Ala
 130 135 140
 Ala Gln Glu Glu Ala Ala Lys Lys
 145 150

<210> 565
 <211> 51
 <212> PRT
 <213> Homo sapiens

<400> 565
 Glu Arg Gly Val Ser Ile Asn Gln Phe Cys Lys Glu Phe Asn Glu Arg
 1 5 10 15
 Thr Lys Asp Ile Lys Glu Gly Ile Pro Leu Pro Thr Lys Ile Leu Val
 20 25 30
 Lys Pro Asp Arg Thr Phe Glu Ile Lys Ile Gly Gln Pro Thr Val Ser
 35 40 45
 Tyr Phe Leu
 50

<210> 566
 <211> 49
 <212> PRT
 <213> Homo sapiens

<400> 566
 Lys Ala Ala Ala Gly Ile Glu Lys Gly Ala Arg Gln Thr Gly Lys Glu
 1 5 10 15
 Val Ala Gly Leu Val Thr Leu Lys His Val Tyr Glu Ile Ala Arg Ile
 20 25 30
 Lys Ala Gln Asp Glu Ala Phe Ala Leu Gln Asp Val Pro Leu Ser Ser
 35 40 45
 Val

<210> 567
 <211> 52
 <212> PRT
 <213> Homo sapiens

<400> 567
 Val Arg Ser Ile Ile Gly Ser Ala Arg Ser Leu Gly Ile Arg Val Val

345

1 5 10 15
 Lys Asp Leu Ser Ser Glu Glu Leu Ala Ala Phe Gln Lys Glu Arg Ala
 20 25 30
 Ile Phe Leu Ala Ala Gln Lys Glu Ala Asp Leu Ala Ala Gln Glu Glu
 35 40 45
 Ala Ala Lys Lys
 50

 <210> 568
 <211> 270
 <212> PRT
 <213> Homo sapiens

 <400> 568
 Ala Val Tyr Thr Tyr His Glu Lys Lys Lys Asp Thr Ala Ala Ser Gly
 1 5 10 15
 Tyr Gly Thr Gln Asn Ile Arg Leu Ser Arg Asp Ala Val Lys Asp Phe
 20 25 30
 Asp Cys Cys Cys Leu Ser Leu Gln Pro Cys His Asp Pro Val Val Thr
 35 40 45
 Pro Asp Gly Tyr Leu Tyr Glu Arg Glu Ala Ile Leu Glu Tyr Ile Leu
 50 55 60
 His Gln Lys Lys Glu Ile Ala Arg Gln Met Lys Ala Tyr Glu Lys Gln
 65 70 75 80
 Arg Gly Thr Arg Arg Glu Glu Gln Lys Glu Leu Gln Arg Ala Ala Ser
 85 90 95
 Gln Asp His Val Arg Gly Phe Leu Glu Lys Glu Ser Ala Ile Val Ser
 100 105 110
 Arg Pro Leu Asn Pro Phe Thr Ala Lys Ala Leu Ser Gly Thr Ser Pro
 115 120 125
 Asp Asp Val Gln Pro Gly Pro Ser Val Gly Pro Pro Ser Lys Asp Lys
 130 135 140
 Asp Lys Val Leu Pro Ser Phe Trp Ile Pro Ser Leu Thr Pro Glu Ala
 145 150 155 160
 Lys Ala Thr Lys Leu Glu Lys Pro Ser Arg Thr Val Thr Cys Pro Met
 165 170 175
 Ser Gly Lys Pro Leu Arg Met Ser Asp Leu Thr Pro Val His Phe Thr
 180 185 190
 Pro Leu Asp Ser Ser Val Asp Arg Val Gly Leu Ile Thr Arg Ser Glu
 195 200 205
 Arg Tyr Val Cys Ala Val Thr Arg Asp Ser Leu Ser Asn Ala Thr Pro

346

210	215	220
Cys Ala Val Leu Arg Pro Ser Gly Ala Val Val Thr Leu Glu Cys Val		
225	230	235 240
Glu Lys Leu Ile Arg Lys Asp Met Val Asp Pro Val Thr Gly Asp Lys		
	245	250 255
Leu Thr Asp Arg Asp Ile Ile Val Leu Gln Arg Gly Gly Thr		
	260	265 270

<210> 569
 <211> 54
 <212> PRT
 <213> Homo sapiens

<400> 569
 Tyr Leu Tyr Glu Arg Glu Ala Ile Leu Glu Tyr Ile Leu His Gln Lys
 1 5 10 15
 Lys Glu Ile Ala Arg Gln Met Lys Ala Tyr Glu Lys Gln Arg Gly Thr
 20 25 30
 Arg Arg Glu Glu Gln Lys Glu Leu Gln Arg Ala Ala Ser Gln Asp His
 35 40 45
 Val Arg Gly Phe Leu Glu
 50

<210> 570
 <211> 64
 <212> PRT
 <213> Homo sapiens

<400> 570
 Phe Thr Ala Lys Ala Leu Ser Gly Thr Ser Pro Asp Asp Val Gln Pro
 1 5 10 15
 Gly Pro Ser Val Gly Pro Pro Ser Lys Asp Lys Asp Lys Val Leu Pro
 20 25 30
 Ser Phe Trp Ile Pro Ser Leu Thr Pro Glu Ala Lys Ala Thr Lys Leu
 35 40 45
 Glu Lys Pro Ser Arg Thr Val Thr Cys Pro Met Ser Gly Lys Pro Leu
 50 55 60

<210> 571
 <211> 56
 <212> PRT
 <213> Homo sapiens

347

<400> 571

Val His Phe Thr Pro Leu Asp Ser Ser Val Asp Arg Val Gly Leu Ile
 1 5 10 15
 Thr Arg Ser Glu Arg Tyr Val Cys Ala Val Thr Arg Asp Ser Leu Ser
 20 25 30
 Asn Ala Thr Pro Cys Ala Val Leu Arg Pro Ser Gly Ala Val Val Thr
 35 40 45
 Leu Glu Cys Val Glu Lys Leu Ile
 50 55

<210> 572

<211> 66

<212> PRT

<213> Homo sapiens

<400> 572

Met Ser Asp Leu Thr Pro Val His Phe Thr Pro Leu Asp Ser Ser Val
 1 5 10 15
 Asp Arg Val Gly Leu Ile Thr Arg Ser Glu Arg Tyr Val Cys Ala Val
 20 25 30
 Thr Arg Asp Ser Leu Ser Asn Ala Thr Pro Cys Ala Val Leu Arg Pro
 35 40 45
 Ser Gly Ala Val Val Thr Leu Glu Cys Val Glu Lys Leu Ile Arg Lys
 50 55 60
 Asp Met
 65

<210> 573

<211> 567

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (409)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 573

Met Asp Thr Ser Glu Asn Arg Pro Glu Asn Asp Val Pro Glu Pro Pro
 1 5 10 15
 Met Pro Ile Ala Asp Gln Val Ser Asn Asp Asp Arg Pro Glu Gly Ser
 20 25 30
 Val Glu Asp Glu Glu Lys Lys Glu Ser Ser Leu Pro Lys Ser Phe Lys
 35 40 45
 Arg Lys Ile Ser Val Val Ser Ala Thr Lys Gly Val Pro Ala Gly Asn
 50 55 60

348

Ser Asp Thr Glu Gly Gly Gln Pro Gly Arg Lys Arg Arg Trp Gly Ala
 65 70 75 80
 Ser Thr Ala Thr Thr Gln Lys Lys Pro Ser Ile Ser Ile Thr Thr Glu
 85 90 95
 Ser Leu Lys Ser Leu Ile Pro Asp Ile Lys Pro Leu Ala Gly Gln Glu
 100 105 110
 Ala Val Val Asp Leu His Ala Asp Asp Ser Arg Ile Ser Glu Asp Glu
 115 120 125
 Thr Glu Arg Asn Gly Asp Asp Gly Thr His Asp Lys Gly Leu Lys Ile
 130 135 140
 Cys Arg Thr Val Thr Gln Val Val Pro Ala Glu Gly Gln Glu Asn Gly
 145 150 155 160
 Gln Arg Glu Glu Glu Glu Glu Lys Glu Pro Glu Ala Glu Pro Pro
 165 170 175
 Val Pro Pro Gln Val Ser Val Glu Val Ala Leu Pro Pro Pro Ala Glu
 180 185 190
 His Glu Val Lys Lys Val Thr Leu Gly Asp Thr Leu Thr Arg Arg Ser
 195 200 205
 Ile Ser Gln Gln Lys Ser Gly Val Ser Ile Thr Ile Asp Asp Pro Val
 210 215 220
 Arg Thr Ala Gln Val Pro Ser Pro Pro Arg Gly Lys Ile Ser Asn Ile
 225 230 235 240
 Val His Ile Ser Asn Leu Val Arg Pro Phe Thr Leu Gly Gln Leu Lys
 245 250 255
 Glu Leu Leu Gly Arg Thr Gly Thr Leu Val Glu Glu Ala Phe Trp Ile
 260 265 270
 Asp Lys Ile Lys Ser His Cys Phe Val Thr Tyr Ser Thr Val Glu Glu
 275 280 285
 Ala Val Ala Thr Arg Thr Ala Leu His Gly Val Lys Trp Pro Gln Ser
 290 295 300
 Asn Pro Lys Phe Leu Cys Ala Asp Tyr Ala Glu Gln Asp Glu Leu Asp
 305 310 315 320
 Tyr His Arg Gly Leu Leu Val Asp Arg Pro Ser Glu Thr Lys Thr Glu
 325 330 335
 Glu Gln Gly Ile Pro Arg Pro Leu His Pro Pro Pro Pro Pro Pro Val
 340 345 350
 Gln Pro Pro Gln His Pro Arg Ala Glu Gln Arg Glu Gln Glu Arg Ala
 355 360 365

349

Val Arg Glu Gln Trp Ala Glu Arg Glu Arg Glu Met Glu Arg Arg Glu
 370 375 380
 Arg Thr Arg Ser Glu Arg Glu Trp Asp Arg Asp Lys Val Arg Glu Gly
 385 390 395 400
 Pro Arg Ser Arg Ser Arg Ser Arg Xaa Arg Arg Arg Lys Glu Arg Ala
 405 410 415
 Lys Ser Lys Glu Lys Lys Ser Glu Lys Lys Glu Lys Ala Gln Glu Glu
 420 425 430
 Pro Pro Ala Lys Leu Leu Asp Asp Leu Phe Arg Lys Thr Lys Ala Ala
 435 440 445
 Pro Cys Ile Tyr Trp Leu Pro Leu Thr Asp Ser Gln Ile Val Gln Lys
 450 455 460
 Glu Ala Glu Arg Ala Glu Arg Ala Lys Glu Arg Glu Lys Arg Arg Lys
 465 470 475 480
 Glu Gln Glu Glu Glu Glu Gln Lys Glu Arg Glu Lys Glu Ala Glu Arg
 485 490 495
 Glu Arg Asn Arg Gln Leu Glu Arg Glu Lys Arg Arg Glu His Ser Arg
 500 505 510
 Glu Arg Asp Arg Glu Arg Glu Arg Glu Arg Glu Arg Asp Arg Gly Asp
 515 520 525
 Arg Asp Arg Asp Arg Glu Arg Asp Arg Glu Arg Gly Arg Glu Arg Asp
 530 535 540
 Arg Arg Asp Thr Lys Arg His Ser Arg Ser Arg Ser Arg Ser Thr Pro
 545 550 555 560
 Val Arg Asp Arg Gly Gly Arg
 565

<210> 574

<211> 48

<212> PRT

<213> Homo sapiens

<400> 574

Glu Asn Asp Val Pro Glu Pro Pro Met Pro Ile Ala Asp Gln Val Ser
 1 5 10 15
 Asn Asp Asp Arg Pro Glu Gly Ser Val Glu Asp Glu Glu Lys Lys Glu
 20 25 30
 Ser Ser Leu Pro Lys Ser Phe Lys Arg Lys Ile Ser Val Val Ser Ala
 35 40 45

350

<210> 575
<211> 37
<212> PRT
<213> Homo sapiens

<400> 575
Val Asp Leu His Ala Asp Asp Ser Arg Ile Ser Glu Asp Glu Thr Glu
1 5 10 15
Arg Asn Gly Asp Asp Gly Thr His Asp Lys Gly Leu Lys Ile Cys Arg
20 25 30
Thr Val Thr Gln Val
35

<210> 576
<211> 55
<212> PRT
<213> Homo sapiens

<400> 576
Pro Gln Val Ser Val Glu Val Ala Leu Pro Pro Pro Ala Glu His Glu
1 5 10 15
Val Lys Lys Val Thr Leu Gly Asp Thr Leu Thr Arg Arg Ser Ile Ser
20 25 30
Gln Gln Lys Ser Gly Val Ser Ile Thr Ile Asp Asp Pro Val Arg Thr
35 40 45
Ala Gln Val Pro Ser Pro Pro
50 55

<210> 577
<211> 55
<212> PRT
<213> Homo sapiens

<400> 577
Leu Lys Glu Leu Leu Gly Arg Thr Gly Thr Leu Val Glu Glu Ala Phe
1 5 10 15
Trp Ile Asp Lys Ile Lys Ser His Cys Phe Val Thr Tyr Ser Thr Val
20 25 30
Glu Glu Ala Val Ala Thr Arg Thr Ala Leu His Gly Val Lys Trp Pro
35 40 45
Gln Ser Asn Pro Lys Phe Leu
50 55

<210> 578
<211> 53
<212> PRT

351

<213> Homo sapiens

<400> 578

Val Asp Arg Pro Ser Glu Thr Lys Thr Glu Glu Gln Gly Ile Pro Arg
 1 5 10 15

Pro Leu His Pro Pro Pro Pro Pro Val Gln Pro Pro Gln His Pro
 20 25 30

Arg Ala Glu Gln Arg Glu Gln Glu Arg Ala Val Arg Glu Gln Trp Ala
 35 40 45

Glu Arg Glu Arg Glu
 50

<210> 579

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 579

Glu Trp Asp Arg Asp Lys Val Arg Glu Gly Pro Arg Ser Arg Ser Arg
 1 5 10 15

Ser Arg Xaa Arg Arg Arg Lys Glu Arg Ala Lys Ser Lys Glu Lys Lys
 20 25 30

Ser Glu Lys Lys Glu Lys Ala Gln Glu Glu Pro Pro Ala Lys Leu Leu
 35 40 45

Asp Asp Leu Phe Arg Lys Thr Lys Ala Ala Pro
 50 55

<210> 580

<211> 64

<212> PRT

<213> Homo sapiens

<400> 580

Pro Leu Thr Asp Ser Gln Ile Val Gln Lys Glu Ala Glu Arg Ala Glu
 1 5 10 15

Arg Ala Lys Glu Arg Glu Lys Arg Arg Lys Glu Gln Glu Glu Glu
 20 25 30

Gln Lys Glu Arg Glu Lys Glu Ala Glu Arg Glu Arg Asn Arg Gln Leu
 35 40 45

Glu Arg Glu Lys Arg Arg Glu His Ser Arg Glu Arg Asp Arg Glu Arg
 50 55 60

352

<210> 581
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 581
 Leu Asp Val Pro Leu Ala Ser Arg Ser Pro Glu Phe Pro Leu Pro Leu
 1 5 10 15
 Met Thr Gln Ser Glu Leu Pro Arg Cys Pro Pro His Pro Gly Ala Arg
 20 25 30

<210> 582
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 582
 Leu Ala Thr Leu Ser Ile Ser Pro Ile Trp Ser Val Leu Ser Leu
 1 5 10 15

<210> 583
 <211> 51
 <212> PRT
 <213> Homo sapiens

<400> 583
 Gly Cys Asp Ser Cys Pro Pro His Leu Pro Arg Glu Ala Phe Ala Gln
 1 5 10 15
 Asp Thr Gln Ala Glu Gly Glu Cys Ser Ser Arg Ala Glu Arg Ala Asp
 20 25 30
 Met Cys Pro Asp Ala Pro Pro Ser Gln Glu Val Pro Glu Gly Pro Gly
 35 40 45
 Ala Ala Pro
 50

<210> 584
 <211> 91
 <212> PRT
 <213> Homo sapiens

<400> 584
 Arg Gly Trp Leu Pro Ser Ser Cys Leu Ser Cys Ala Leu Arg Val Cys
 1 5 10 15

353

Pro Asp Ser Ser Ser Thr Gln Ala Met Gly Met Leu Leu Ala Phe Trp
 20 25 30
 Leu Pro Gly Ala Ser Trp Gln Glu Ala Ala Arg Gly Gln Tyr Ser Glu
 35 40 45
 Asp Glu Asp Thr Asp Thr Asp Glu Tyr Lys Glu Ala Lys Ala Ser Ile
 50 55 60
 Asn Pro Val Thr Gly Arg Val Glu Glu Lys Pro Pro Asn Pro Met Glu
 65 70 75 80
 Gly Met Thr Glu Glu Gln Lys Glu His Glu Ala
 85 90

<210> 585
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 585
 Thr Gln Ala Met Gly Met Leu Leu Ala Phe Trp Leu Pro Gly Ala Ser
 1 5 10 15
 Trp Gln Glu Ala Ala Arg Gly Gln Tyr Ser Glu
 20 25

<210> 586
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 586
 Pro Gln Leu Pro Ser Cys Gly Arg Pro Trp Pro Gly Thr Ala Ser Val
 1 5 10 15
 Phe Gln Ser His Thr Gln Gly Pro Arg Glu Asp Pro Asp Pro Cys Arg
 20 25 30
 Ala Gln Gly Ser Ala Gly Thr His Cys Pro Ile Ser Leu Ser Pro Pro
 35 40 45
 Arg Gln
 50

<210> 587
 <211> 103
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (23)
 <223> Xaa equals any of the naturally occurring L-amino acids

354

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 587

Lys Thr His Pro Arg Ala Leu Trp Ser Ala Gly Pro Ser Cys Ala Leu
 1 5 10 15

Cys Pro Gly Gly Ser Gly Xaa Thr Ser Pro Pro Gln Gly Ala Pro Arg
 20 25 30

Gly Ile Xaa Trp Asp Arg Cys Pro Gln Ile Gln Val Leu Glu Gly Gln
 35 40 45

Arg Val Arg Phe Pro Ser Gln Pro Gln His Pro Ser His Leu Ala Pro
 50 55 60

Arg Gly Gly Cys Gly Trp Arg Pro Asp Ser Arg Pro Leu Leu Pro Thr
 65 70 75 80

Pro Ser Gly Leu Ser Ser Phe Phe Pro Leu Asp Ala Gln Cys Trp Pro
 85 90 95

Trp Arg Thr Val Ser Trp Arg
 100

<210> 588

<211> 200

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (174)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (186)

<223> Xaa equals any of the naturally occurring L-amino acids

355

<400> 588

Ala Gly Ala Pro Gly Gln Gln Ala Arg Leu Gln Tyr Leu Leu Ser Phe
 1 5 10 15
 Gln Gly Glu Gly Ala Pro His Glu Xaa Gly Ala Thr Gly Glu Gly Gly
 20 25 30
 Asp Gly Ala Trp Glu Ala Cys Xaa Cys Xaa Arg Cys Leu Leu Asn Trp
 35 40 45
 Gln Ala Gly Gly Trp Gly Leu Gln Leu Ser Leu Met Trp Leu His Arg
 50 55 60
 Gly Pro Leu Arg Pro Pro Gly Val Arg Trp Thr Pro Trp Ala Phe Leu
 65 70 75 80
 Glu Ala Cys Ser Trp Gly Pro Ala Leu Ser Leu Leu Gly Ser Gly His
 85 90 95
 Ser Leu Pro Gly Thr His Glu Gln Ala Ala Trp Ser Arg Gly Cys Gly
 100 105 110
 Gln His Gly Gln Ser Pro Thr Gln Lys Cys Lys Ser Ser Lys Glu Pro
 115 120 125
 Leu Ala Gln Ala Pro Pro Trp Asp Ser Pro Ala Ala Pro Pro His Gln
 130 135 140
 Gly Phe Ala Asp Val Leu Glu Arg Pro Thr Leu Glu Pro Phe Gly Val
 145 150 155 160
 Leu Ala Pro Pro Val Pro Ser Ala Leu Val Glu Ala Ala Xaa Gln Val
 165 170 175
 Leu Leu Arg Glu Pro Gln Gly Gly Phe Xaa Gly Thr Ala Ala His Arg
 180 185 190
 Ser Arg Cys Trp Lys Gly Ser Gly
 195 200

<210> 589

<211> 145

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (81)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

356

<222> (125)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (142)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 589

Met	Gln	Leu	Leu	Phe	Leu	Leu	Pro	His	Pro	Ser	Pro	Gln	Leu	His	Ala
1				5					10					15	

Ser	Leu	Pro	His	Ser	Ala	Ala	Leu	Pro	Cys	Pro	Arg	Gly	Glu	Ser	Leu
			20					25					30		

Thr	Thr	Ala	Ser	Pro	Ala	Gly	Ala	Ala	Gly	Arg	Xaa	Asp	Ala	Val	Pro
		35					40					45			

Arg	Cys	Arg	His	Gln	Ala	Gly	Arg	Gly	Trp	Val	Pro	Arg	Gly	Pro	Cys
	50					55					60				

Glu	Arg	Gly	Gly	Gly	Asp	Arg	Gly	Lys	Pro	Arg	Ala	Val	Ala	Trp	Asp
65					70				75						80

Xaa	Gly	Ser	Leu	Arg	Trp	Ala	Val	Trp	Ser	Ala	Arg	Ala	Gly	Gln	Gly
				85					90					95	

Arg	Ser	Ser	Glu	Pro	Ala	Pro	Leu	Ala	Ser	Arg	Arg	Gly	Tyr	Ser	Thr
			100					105					110		

Cys	Cys	Leu	Ser	Arg	Gly	Lys	Gly	Leu	Pro	Met	Arg	Xaa	Gly	Arg	Arg
		115					120					125			

Gly	Arg	Gly	Val	Met	Val	Pro	Gly	Lys	Pro	Ala	Cys	Ala	Xaa	Gly	Ala
	130						135					140			

Cys
145

<210> 590

<211> 34

<212> PRT

<213> Homo sapiens

<400> 590

Gln	His	Pro	Ser	His	Leu	Ala	Pro	Arg	Gly	Gly	Cys	Gly	Trp	Arg	Pro
1				5					10					15	

Asp	Ser	Arg	Pro	Leu	Leu	Pro	Thr	Pro	Ser	Gly	Leu	Ser	Ser	Phe	Phe
			20					25						30	

Pro Leu

<210> 591

<211> 30

357

<212> PRT

<213> Homo sapiens

<400> 591

Gly Val Arg Trp Thr Pro Trp Ala Phe Leu Glu Ala Cys Ser Trp Gly
1 5 10 15

Pro Ala Leu Ser Leu Leu Gly Ser Gly His Ser Leu Pro Gly
20 25 30

<210> 592

<211> 28

<212> PRT

<213> Homo sapiens

<400> 592

Trp Asp Ser Pro Ala Ala Pro Pro His Gln Gly Phe Ala Asp Val Leu
1 5 10 15

Glu Arg Pro Thr Leu Glu Pro Phe Gly Val Leu Ala
20 25

<210> 593

<211> 28

<212> PRT

<213> Homo sapiens

<400> 593

Arg Ser Ser Glu Pro Ala Pro Leu Ala Ser Arg Arg Gly Tyr Ser Thr
1 5 10 15

Cys Cys Leu Ser Arg Gly Lys Gly Leu Pro Met Arg
20 25

<210> 594

<211> 42

<212> PRT

<213> Homo sapiens

<400> 594

Pro Gly Phe Arg Gly Pro Ser Gly Ser Leu Gly Cys Ser Phe Phe Pro
1 5 10 15

Arg Ser Leu Gly Arg Val Leu Pro Pro Gly Cys Gln Arg Pro Gly Ala
20 25 30

His Ala Asp Ser Ser Pro Pro Pro Thr Pro
35 40

<210> 595

<211> 84

<212> PRT

<213> Homo sapiens

358

<400> 595

Glu Asp Leu Lys Lys Pro Asp Pro Ala Ser Leu Arg Ala Ala Ser Cys
 1 5 10 15

Gly Glu Gly Lys Lys Arg Lys Ala Cys Lys Asn Cys Thr Cys Gly Leu
 20 25 30

Ala Glu Glu Leu Glu Lys Glu Lys Ser Arg Glu Gln Met Ser Ser Gln
 35 40 45

Pro Lys Ser Ala Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe Arg Cys
 50 55 60

Ala Ser Cys Pro Tyr Leu Gly Met Pro Ala Phe Lys Pro Gly Glu Lys
 65 70 75 80

Val Leu Leu Ser

<210> 596

<211> 90

<212> PRT

<213> Homo sapiens

<400> 596

Glu Asp Leu Lys Lys Pro Asp Pro Ala Ser Leu Arg Ala Ala Ser Cys
 1 5 10 15

Gly Glu Gly Lys Lys Arg Lys Ala Cys Lys Asn Cys Thr Cys Gly Leu
 20 25 30

Ala Glu Glu Leu Glu Lys Glu Lys Ser Arg Glu Gln Met Ser Ser Gln
 35 40 45

Pro Lys Ser Ala Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe Arg Cys
 50 55 60

Ala Ser Cys Pro Tyr Leu Gly Met Pro Ala Phe Lys Pro Gly Glu Lys
 65 70 75 80

Val Leu Leu Ser Asp Ser Asn Leu His Asp
 85 90

<210> 597

<211> 34

<212> PRT

<213> Homo sapiens

<400> 597

Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe Arg Cys Ala Ser Cys Pro
 1 5 10 15

Tyr Leu Gly Met Pro Ala Phe Lys Pro Gly Glu Lys Val Leu Leu Ser
 20 25 30

Asp Ser

359

<210> 598

<211> 25

<212> PRT

<213> Homo sapiens

<400> 598

Ser	Cys	Gly	Glu	Gly	Lys	Lys	Arg	Lys	Ala	Cys	Lys	Asn	Cys	Thr	Cys
1				5					10					15	

Gly	Leu	Ala	Glu	Glu	Leu	Glu	Lys	Glu
			20					25

<210> 599

<211> 21

<212> PRT

<213> Homo sapiens

<400> 599

Ser	Gln	Pro	Lys	Ser	Ala	Cys	Gly	Asn	Cys	Tyr	Leu	Gly	Asp	Ala	Phe
1				5					10					15	

Arg	Cys	Ala	Ser	Cys
			20	

<210> 600

<211> 17

<212> PRT

<213> Homo sapiens

<400> 600

Arg	Glu	Ala	Gly	Gln	Asn	Ser	Glu	Arg	Gln	Tyr	Val	Ser	Leu	Ser	Arg
1				5					10					15	

Asp

<210> 601

<211> 16

<212> PRT

<213> Homo sapiens

<400> 601

Cys	Cys	Cys	Val	Ser	Lys	Asp	Gln	Gly	Ile	Met	Gly	Pro	Gly	Phe	Arg
1				5					10					15	

<210> 602

<211> 103

<212> PRT

360

<213> Homo sapiens

<400> 602

His Ser Val Thr Glu Leu Gln Thr Pro Ala Leu Ser Leu Ile Ser Ala
 1 5 10 15

Met Leu Pro Pro Ser Cys Leu Ser Glu Leu Leu Val Tyr Ser Ile Leu
 20 25 30

Cys Asp Thr Ser Gln Val Ala His Asn Leu Leu Arg Ala Pro Glu Asp
 35 40 45

Ser Leu Thr Gly Cys Cys Asp Asp Ile Gln Cys Pro Ser Ala Pro Phe
 50 55 60

His Pro Gln Pro His Leu Thr Val Ala Leu His Leu Cys Pro Val Val
 65 70 75 80

Ile Tyr Val Asn Leu Gln Val Leu Asn Leu Leu His Ile Leu Thr Tyr
 85 90 95

Leu Glu Ile Leu His Val Leu
 100

<210> 603

<211> 24

<212> PRT

<213> Homo sapiens

<400> 603

Leu Leu Val Tyr Ser Ile Leu Cys Asp Thr Ser Gln Val Ala His Asn
 1 5 10 15

Leu Leu Arg Ala Pro Glu Asp Ser
 20

<210> 604

<211> 26

<212> PRT

<213> Homo sapiens

<400> 604

Leu Thr Val Ala Leu His Leu Cys Pro Val Val Ile Tyr Val Asn Leu
 1 5 10 15

Gln Val Leu Asn Leu Leu His Ile Leu Thr
 20 25

<210> 605

<211> 55

<212> PRT

<213> Homo sapiens

<400> 605

Phe Phe Asn Ala Leu Tyr Val Phe Arg Lys Pro Gln Ala Ile Phe Asp

```

1           5           10           15
Ser Glu Lys Glu Asn Lys Arg Lys Asn Pro Thr Lys Tyr Asn Asn Pro
      20           25           30
Leu Arg Tyr Ile Tyr Phe Lys Val Lys Leu Ile Phe Gln Phe Ile Pro
      35           40           45
Leu Ala Asn Tyr Lys Ile Lys
      50           55

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<400> 606
Glu Ser Ser Gly Gln Ala Arg Thr Leu Ala Asp Pro Gly Pro Gly Trp
  1             5             10             15

Pro Arg Gln Gln Gly Met Cys Phe Gly Ser Leu Thr Gly Leu Ser Thr
      20             25             30

Thr Pro His Gly Phe Leu Thr Val Ser Ala Glu Ala Asp Pro Arg Leu
      35             40             45

Ile Glu Ser Leu Ser Gln Met Leu Ser Met Gly Phe Ser Asp Glu Gly
  50             55             60

Gly Trp Leu Thr Arg Leu Leu Gln Thr Lys Asn Tyr Asp Ile Gly Ala
  65             70             75             80

Ala Leu Asp Thr Ile Gln Tyr Ser Lys His
      85             90

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<400> 607
Tyr Ser Met Val Tyr Ile Tyr His Ile Phe Phe Ile His Ser Leu Leu
  1             5             10             15
Asp Gly Gln Leu Gly Trp Phe His Ile Phe Ala Ile Val Ser Cys Ala
      20             25             30
Ala Pro Asp Ile Ile Phe Asn Ser Phe Ala Phe Ser Thr Tyr Ile Ser
      35             40             45
Lys Ser Cys Ser Phe Tyr Leu Gln Asn Val Ser Cys Ile His Ser Ser
      50             55             60
Leu Ser Ile Phe Asn Leu Phe Gln Cys Pro Ile Ile Ser Cys Met Glu
      65             70             75             80

```

362

Glu Cys Asn Asn Trp Leu Thr Gly Leu Phe Leu His Phe Lys Ile Lys
 85 90 95

Arg Cys Asp Arg
 100

<210> 608
 <211> 67
 <212> PRT
 <213> Homo sapiens

<400> 608
 Leu Ser Pro Ser Pro Arg Cys Cys Pro Trp Ala Ser Leu Met Lys Ala
 1 5 10 15

Ala Gly Ser Pro Gly Ser Cys Arg Pro Arg Thr Met Thr Ser Glu Arg
 20 25 30

Leu Trp Thr Pro Ser Ser Ile Gln Ser Ile Pro Arg Arg Cys Asp His
 35 40 45

Phe Cys Pro Pro Leu Leu Arg Ala Pro Leu Leu Ser His Ser Cys Val
 50 55 60

Lys Leu Ala
 65

<210> 609
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 609
 Gly Trp Pro Arg Gln Gln Gly Met Cys Phe Gly Ser Leu Thr Gly Leu
 1 5 10 15

Ser Thr Thr Pro His Gly Phe Leu Thr Val Ser Ala Glu Ala Asp Pro
 20 25 30

Arg Leu

<210> 610
 <211> 33
 <212> PRT
 <213> Homo sapiens

<400> 610
 Leu Gly Trp Phe His Ile Phe Ala Ile Val Ser Cys Ala Ala Pro Asp
 1 5 10 15

Ile Ile Phe Asn Ser Phe Ala Phe Ser Thr Tyr Ile Ser Lys Ser Cys
 20 25 30

Ser

363

<210> 611
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 611
 Ser Leu Ser Ile Phe Asn Leu Phe Gln Cys Pro Ile Ile Ser Cys Met
 1 5 10 15
 Glu Glu Cys Asn Asn Trp Leu Thr Gly
 20 25

<210> 612
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 612
 Leu Met Lys Ala Ala Gly Ser Pro Gly Ser Cys Arg Pro Arg Thr Met
 1 5 10 15
 Thr Ser Glu Arg Leu Trp Thr Pro Ser Ile Gln Ser Ile
 20 25 30

<210> 613
 <211> 152
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (71)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 613
 Ser Ser Ser Ser Pro Arg Arg Pro Arg Glu Leu Leu Gly Ser Leu Lys
 1 5 10 15
 Thr Pro Leu Val Arg Pro His Ser Ala Pro Leu Asp Leu Pro Gly Ser
 20 25 30

Phe Cys Xaa His Thr Ala Asp Pro Met Gly Ala Leu His Thr Arg Phe
 35 40 45

Trp Gly Arg Gln Thr Trp Ile His Arg Lys Leu Arg Leu His Gly Thr
 50 55 60

Ser Arg Leu Ala Ser Lys Xaa Gly Ile Gln Phe Leu Arg Asn Pro Ser

65	70								75								80			
Lys Thr His Thr Pro Arg Asp Ala Ala Phe Arg Asp Pro Gly Gln Thr																				
	85								90								95			
Pro Asp Pro Gln Ser Leu Gln Ala Pro Ser Pro Ser Lys Cys Ser Ala																				
	100								105								110			
Pro Asn Arg Ala Thr Ser Val Trp Ser Leu Lys Pro Arg Leu Leu Tyr																				
	115								120								125			
Lys His Arg Pro Ser Ser Asp Lys Thr Pro Pro Pro Gly Arg Gln Ala																				
	130								135								140			
Pro Leu Leu Phe Phe Ser Ala Gly																				
145	150																			

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<400> 614
Phe Leu Arg Asn Pro Ser Lys Thr His Thr Pro Arg Asp Ala Ala Phe
 1                5                10                15

Arg Asp Pro Gly Gln Thr Pro Asp Pro Gln Ser Leu Gln Ala
      20                25                30

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<220>
<221> SITE
<222> (43)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>  
<221> SITE  
<222> (155)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 615
Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val
  1                      5                      10                      15

Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu
          20                      25                      30

Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Xaa Ala Val Arg Ser His
          35                      40                      45

His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile
  50                      55                      60

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365

Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala
65 70 75 80

Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe
85 90 95

His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met
100 105 110

Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val
115 120 125

Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly
130 135 140

Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Xaa Ser Thr Gly Trp
145 150 155

<210> 616

<211> 35

<212> PRT

<213> Homo sapiens

<400> 616

Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile Tyr Phe Asp Gln Val
1 5 10 15

Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala Ser Gly Ser Phe Val
20 25 30

Ala Pro Val
35

<210> 617

<211> 25

<212> PRT

<213> Homo sapiens

<400> 617

Asn Asp Pro Asp Val Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu
1 5 10 15

Pro Leu Asp Pro Gly Asp Arg Val Ser
20 25

<210> 618

<211> 11

<212> PRT

<213> Homo sapiens

<400> 618

Phe His Val Val Lys Val Tyr Asn Arg Gln Thr
1 5 10

366

<210> 619
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 619
 Ile Tyr Phe Asp Gln Val Leu Val Asn
 1 5

<210> 620
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 620
 Glu Ser Arg Glu Arg Ser Gly Asn Arg Arg Gly Ala Glu Asp Arg Gly
 1 5 10 15

Thr Cys Gly Leu Gln Ser Pro Ser Ala
 20 25

<210> 621
 <211> 70
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (30)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 621
 Glu Met Pro Gln Phe Tyr Phe Phe Leu Lys Leu Gly Cys Leu Ala Gln
 1 5 10 15

Val Pro Met Gln Arg Gly Gly Ile Gly Ala Arg Gly Ser Xaa Xaa Pro
 20 25 30

Ala Xaa Ala Val Xaa Gly Ala Arg Glu Gly Arg Arg Lys Leu Ser Gly
 35 40 45

367

Ala Gly Phe Leu Cys Leu Lys Asp Leu Gly Pro Ser Glu Arg Glu Asp
 50 55 60

Glu Glu Ala Arg Glu Thr
 65 70

<210> 622

<211> 27

<212> PRT

<213> Homo sapiens

<400> 622

Met Pro Gln Phe Tyr Phe Phe Leu Lys Leu Gly Cys Leu Ala Gln Val
 1 5 10 15

Pro Met Gln Arg Gly Gly Ile Gly Ala Arg Gly
 20 25

<210> 623

<211> 185

<212> PRT

<213> Homo sapiens

<400> 623

Gln Ala Thr Cys Ser Ala Ser Gly Ser Pro Gly Gln Phe Gly Gly Cys
 1 5 10 15

Thr Pro Ser Pro His Gly Thr Gly Ser Cys Arg His Pro Gly Gln Gly
 20 25 30

Leu Arg Arg Ser Gln Arg Pro Gly Gln Ser His Arg Pro Arg Ser Pro
 35 40 45

Gly Pro Gly Arg Ser Arg Trp Pro His Trp Cys His Cys Arg Phe Pro
 50 55 60

Leu Leu Ala His Gly Gly Gly Phe Gly Pro Gln Gln Met Pro Leu Ala
 65 70 75 80

Gln Gly Val Pro Leu Pro Gly Leu Leu Pro Arg Ala Pro Leu Gln Gln
 85 90 95

Leu Gly Gln Ala His Arg Pro Pro Gly Thr Pro Pro Pro Ala Gly Arg
 100 105 110

Ala Leu Thr Pro Pro Gly Pro Thr Arg Pro Pro Gly Pro Glu Ala Pro
 115 120 125

Glu Pro Arg Ala Ala Arg Asp Cys Val Gly Asp Leu Val Ala Ser Val
 130 135 140

Ala Trp Leu Pro Thr Trp Leu Arg Gly Ser Ala Thr His Lys Cys Pro
 145 150 155 160

Gly Leu Leu Pro Leu Phe Cys Phe Arg Ser Ser Pro Trp Ile Leu Thr

368

165

170

175

Ala Gly Thr Leu Ile Val Cys Pro Leu
180 185

<210> 624

<211> 25

<212> PRT

<213> Homo sapiens

<400> 624

Gly Cys Thr Pro Ser Pro His Gly Thr Gly Ser Cys Arg His Pro Gly
1 5 10 15

Gln Gly Leu Arg Arg Ser Gln Arg Pro
20 25

<210> 625

<211> 26

<212> PRT

<213> Homo sapiens

<400> 625

Ser Arg Trp Pro His Trp Cys His Cys Arg Phe Pro Leu Leu Ala His
1 5 10 15

Gly Gly Gly Phe Gly Pro Gln Gln Met Pro
20 25

<210> 626

<211> 28

<212> PRT

<213> Homo sapiens

<400> 626

Asp Cys Val Gly Asp Leu Val Ala Ser Val Ala Trp Leu Pro Thr Trp
1 5 10 15

Leu Arg Gly Ser Ala Thr His Lys Cys Pro Gly Leu
20 25

<210> 627

<211> 115

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 627

Asp Asp Arg Pro Arg Val Gln His Gln Ala His Leu Asp Ser Leu Ala
1 5 10 15

369

Val Val His Leu His His Met Glu Pro Glu Ala Val Asp Thr Pro Asp
 20 25 30

Arg Gly Tyr Glu Gly Ala Arg Gly Pro Val Lys Ala Thr Ala Leu Val
 35 40 45

His Gln Asp Leu Val Glu Val Asp Gly Pro Thr Gly Ala Ile Ala Gly
 50 55 60

Phe Pro Cys Trp Leu Met Val Val Ala Ser Asp Arg Xaa Lys Cys His
 65 70 75 80

Ser Pro Arg Gly Cys Leu Ser Gln Gly Cys Ser Pro Gly Pro Pro Cys
 85 90 95

Ser Ser Ser Ala Arg Leu Thr Asp His Gln Ala Leu Pro Leu Gln Gln
 100 105 110

Asp Gly Leu
 115

<210> 628
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 628
 Tyr Glu Gly Ala Arg Gly Pro Val Lys Ala Thr Ala Leu Val His Gln
 1 5 10 15

Asp Leu Val Glu Val Asp Gly Pro Thr Gly Ala Ile Ala Gly Phe
 20 25 30

<210> 629
 <211> 159
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (22)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 629
 Met Ala Pro Leu Val Pro Leu Pro Val Ser Pro Ala Gly Ser Trp Trp
 1 5 10 15

Trp Leu Arg Thr Ala Xaa Asn Ala Thr Arg Pro Gly Gly Ala Ser Pro
 20 25 30

Arg Ala Ala Pro Pro Gly Pro Pro Ala Ala Ala Arg Pro Gly Ser Gln
 35 40 45

Thr Thr Arg His Ser Pro Ser Ser Arg Thr Gly Ser Asp Pro Ser Trp
 50 55 60

370

Ala His Pro Ala Pro Arg Ala Arg Ser Thr Arg Thr Lys Gly Ser Pro
65 70 75 80

Gly Leu Cys Arg Gly Pro Gly Ser Gln Cys Gly Leu Ala Pro Asn Met
85 90 95

Ala Glu Gly Leu Cys Asn Pro Gln Val Pro Arg Ser Ser Ala Pro Leu
100 105 110

Leu Phe Pro Leu Leu Ser Leu Asp Ser His Arg Arg His Pro Asp Ser
115 120 125

Leu Pro Ser Leu Gly Ser Leu Asn Pro Leu Ser Ile Pro Val Ser Gln
130 135 140

Leu Cys Pro Ala Ser His Ser Tyr Ser Cys Cys His Cys Ser Ser
145 150 155

<210> 630
<211> 29
<212> PRT
<213> Homo sapiens

<400> 630
Ser Ser Arg Thr Gly Ser Asp Pro Ser Trp Ala His Pro Ala Pro Arg
1 5 10 15

Ala Arg Ser Thr Arg Thr Lys Gly Ser Pro Gly Leu Cys
20 25

<210> 631
<211> 27
<212> PRT
<213> Homo sapiens

<400> 631
Arg Arg His Pro Asp Ser Leu Pro Ser Leu Gly Ser Leu Asn Pro Leu
1 5 10 15

Ser Ile Pro Val Ser Gln Leu Cys Pro Ala Ser
20 25

<210> 632
<211> 31
<212> PRT
<213> Homo sapiens

<400> 632
Ser Thr His Ala Ser Gly Pro Pro Ala Pro Glu Arg Leu Cys Leu Pro
1 5 10 15

Glu Arg Gly Thr Ala Pro Trp Gly Arg Arg Ala Asn Asp Ala Ala
20 25 30

371

<210> 633
 <211> 181
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (56)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (57)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (60)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (83)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (84)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (165)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 633
 Val Arg Arg Trp Trp Leu Arg Thr Met Gly Ala Ala Ala His Cys Thr
 1 5 10 15

Pro Glu Gln Arg Arg Pro Arg Arg Pro Ala Thr Ile Leu Gly Met Asp
 20 25 30

Thr Gln Asn Ile Leu His Thr Arg Leu Ser Leu Cys Ser Leu Ser Trp
 35 40 45

Val Ser Leu Ala Ser Ser Phe Xaa Xaa Leu Ala Xaa Arg Arg Lys Ala
 50 55 60

Ile Val Val Gln Gln Lys Gln Ser Lys Ile Ser Lys Lys Lys Lys Val
 65 70 75 80

Glu Lys Xaa Xaa Leu Asn Asp Ser Val Asn Glu Asn Ser Asp Thr Val
 85 90 95

Gly Gln Ile Val His Tyr Ile Met Lys Asn Glu Ala Asn Ala Asp Val
 100 105 110

372

Leu Lys Ala Met Val Ala Asp Asn Ser Leu Tyr Asp Pro Glu Ser Pro
 115 120 125

Val Thr Pro Ser Thr Pro Gly Ser Pro Pro Val Ser Pro Gly Leu Cys
 130 135 140

His Gln Gly Gly Arg Gln Gly Ser Thr Ser Val Ala Ile Ile Cys Ile
 145 150 155 160

Arg Trp Ala Val Xaa Ser Arg Gly Met Cys Val Ile Gly Val Gly Thr
 165 170 175

Ser Gly Gly Thr Leu
 180

<210> 634

<211> 29

<212> PRT

<213> Homo sapiens

<400> 634

Ile Met Lys Asn Glu Ala Asn Ala Asp Val Leu Lys Ala Met Val Ala
 1 5 10 15

Asp Asn Ser Leu Tyr Asp Pro Glu Ser Pro Val Thr Pro
 20 25

<210> 635

<211> 143

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 635

His Cys His Leu Trp Ala Ser Gly Ser Cys Leu Ala Cys Phe Phe Pro
 1 5 10 15

Gly Gly Leu Thr Arg Asp Ala Ala Gln Gln His Val Thr Lys Ser Tyr
 20 25 30

Ser Pro Pro Tyr Leu Ser Gln Thr Ser His Ser Cys Leu Val Phe Gln
 35 40 45

Pro Val Leu Trp Pro Glu Tyr Thr Phe Trp Asn Leu Phe Glu Ala Ile
 50 55 60

Leu Gln Phe Gln Met Asn His Ser Val Leu Gln Gln Xaa Gly Pro Arg
 65 70 75 80

His Val Cys Arg Gly Ala Glu Glu Ala Ala Ala Gly Glu Gly Pro Gly
 85 90 95

373

Tyr Ser Asp Arg Ala Ala Ala Ala Arg Gly Ala Pro Ser Gln Trp Gly
100 105 110

Arg Pro Ala Pro Lys Asp Thr Leu Ala Gln Thr Leu Gly Gln Thr Gly
115 120 125

Arg Ala Ser Pro Arg Leu Pro Ala Gly Leu Gly Thr Gln Ala Ser
130 135 140

<210> 636

<211> 28

<212> PRT

<213> Homo sapiens

<400> 636

Pro Ala Pro Lys Asp Thr Leu Ala Gln Thr Leu Gly Gln Thr Gly Arg
1 5 10 15

Ala Ser Pro Arg Leu Pro Ala Gly Leu Gly Thr Gln
20 25

<210> 637

<211> 85

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 637

Thr Ile Ala Cys Phe Ser Xaa Lys Ala Arg Asp Met Tyr Ala Glu Glu
1 5 10 15

Arg Lys Arg Gln Gln Leu Glu Arg Asp Gln Ala Thr Val Thr Glu Gln
20 25 30

Leu Leu Arg Glu Gly Leu Gln Ala Ser Gly Asp Ala Gln Leu Arg Arg
35 40 45

Thr Arg Leu His Lys Leu Ser Ala Arg Arg Glu Glu Arg Val Gln Gly
50 55 60

Phe Leu Gln Ala Leu Glu Leu Lys Arg Ala Asp Trp Leu Ala Arg Leu
65 70 75 80

Gly Thr Ala Ser Ala
85

<210> 638

<211> 28

<212> PRT

<213> Homo sapiens

374

<400> 638

Leu Arg Arg Thr Arg Leu His Lys Leu Ser Ala Arg Arg Glu Glu Arg
 1 5 10 15

Val Gln Gly Phe Leu Gln Ala Leu Glu Leu Lys Arg
 20 25

<210> 639

<211> 112

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 639

Lys Met Asn Ser Ile Pro Trp Gln Ile Pro Lys Ile Thr Pro Xaa Leu
 1 5 10 15

Asp Ala Asn Leu Val Ile Val Glu Cys Lys Pro Leu Trp Phe Cys Ile
 20 25 30

Gly Thr Ile Lys Gln Leu Lys Leu Trp Asn Gln Val Phe Met Gly Phe
 35 40 45

Lys Ser Met Phe Phe Arg Ile Gly Lys Leu Asn Tyr Leu Phe Thr Ile
 50 55 60

Pro Tyr Cys Tyr Leu Phe Ile Asp Asn Ile Leu Gly Ile Phe Tyr Ser
 65 70 75 80

Ile Leu Gly Ala Gln Gly Ile Lys Tyr Asn Phe Tyr Ile Gln Arg Ile
 85 90 95

Phe Thr Cys Leu Leu Asn Leu Asn Leu Lys Ile His Ser Asn Leu Ala
 100 105 110

<210> 640

<211> 27

<212> PRT

<213> Homo sapiens

<400> 640

Leu Trp Phe Cys Ile Gly Thr Ile Lys Gln Leu Lys Leu Trp Asn Gln
 1 5 10 15

Val Phe Met Gly Phe Lys Ser Met Phe Phe Arg
 20 25

<210> 641

375

<211> 26
<212> PRT
<213> Homo sapiens

<400> 641
Tyr Ser Ile Leu Gly Ala Gln Gly Ile Lys Tyr Asn Phe Tyr Ile Gln
1 5 10 15
Arg Ile Phe Thr Cys Leu Leu Asn Leu Asn
20 25

<210> 642
<211> 9
<212> PRT
<213> Homo sapiens

<400> 642
Thr Phe Lys Leu Val Arg Phe Leu Glu
1 5

<210> 643
<211> 32
<212> PRT
<213> Homo sapiens

<400> 643
Pro Arg Ser Arg Pro Ala Leu Arg Pro Gly Arg Gln Arg Pro Pro Ser
1 5 10 15
His Ser Ala Thr Ser Gly Val Leu Arg Pro Arg Lys Lys Pro Asp Pro
20 25 30

<210> 644
<211> 120
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (105)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 644
Arg Lys Ser Phe Ala Lys Pro Val Leu Trp Thr Asn Ala Ile Gln Ala
1 5 10 15
Gly Arg Gly Arg Val Leu Cys Tyr Thr Arg Pro Pro Pro Ala Ser Ser

376

	20		25		30
Ser	Phe	Ser	Ala	Leu	Val
	35		40		45
Pro	Asp	Gly	Asn	Arg	Met
Glu	Gly	Leu	Arg		
Thr	Tyr	Phe	Leu	Asn	Ala
	50		55		60
Pro	Gly	Thr	Asp	Tyr	Leu
Tyr	Leu	Tyr	Leu		
Phe	Pro	Phe	Ser	Phe	Thr
	65		70		75
Cys	Leu	Thr	Val	Arg	
Trp	Ala	Phe	Glu	Ser	Leu
	85		90		95
Pro	Gln	Asn	Arg	Pro	Glu
Arg	Trp				
Ala	Ser	His	Pro	Leu	Pro
	100		105		110
Pro	Asp	Asn			
Gln	Val	Xaa	Met	Ser	Ala
	115		120		

<210> 645
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 645
 Gly Asn Arg Met Glu Gly Leu Arg Thr Tyr Phe Leu Asn Ala Phe Asp
 1 5 10 15
 Pro Gly Thr Asp Tyr Leu Tyr Leu Phe
 20 25

<210> 646
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 646
 Phe Gln His Cys Leu Thr Val Arg Trp Ala Phe Glu Ser Leu Gln Val
 1 5 10 15
 Pro Gln Asn Arg Pro Glu Arg Trp Ala Ser His Pro Leu Pro
 20 25 30

<210> 647
 <211> 31
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <220>

377

<221> SITE

<222> (13)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 647

Met Thr Leu Ile Thr Pro Ser Xaa Lys Leu Thr Phe Xaa Lys Gly Asn
 1 5 10 15

Lys Ser Trp Ser Ser Arg Ala Cys Ser Ser Thr Leu Val Asp Pro
 20 25 30

<210> 648

<211> 14

<212> PRT

<213> Homo sapiens

<400> 648

Phe Leu Phe Leu His Ala Val Asp Pro Trp Pro Ser Asn Gly
 1 5 10

<210> 649

<211> 61

<212> PRT

<213> Homo sapiens

<400> 649

Trp Ser Cys Gln Ser Gly Val Phe Leu Val Phe Thr Gly Cys Ser Val
 1 5 10 15

Leu Cys Gln Met Leu Ser Gly Ala Val Val Val Trp Arg Arg Ser Ala
 20 25 30

Pro Glu Asp Ser Ala Val Trp Gln Ala Ser Ile Asn Lys Pro Arg Gly
 35 40 45

Lys Gly Arg His Gly Ile Lys Gly Glu Asn Thr Ser Val
 50 55 60

<210> 650

<211> 35

<212> PRT

<213> Homo sapiens

<400> 650

Leu Val Phe Thr Gly Cys Ser Val Leu Cys Gln Met Leu Ser Gly Ala
 1 5 10 15

Val Val Val Trp Arg Arg Ser Ala Pro Glu Asp Ser Ala Val Trp Gln
 20 25 30

Ala Ser Ile
 35

<210> 651

378

<211> 51
 <212> PRT
 <213> Homo sapiens

<400> 651
 Gly His Pro Ser Pro Ala Leu Ser Ile Ala Pro Ser Asp Gly Ser Gln
 1 5 10 15
 Leu Pro Cys Asp Glu Val Pro Tyr Gly Glu Ala His Val Thr Arg Tyr
 20 25 30
 Cys Lys Lys Pro Leu Thr Asn Ser His Leu Glu Thr Glu Ala Gln Ser
 35 40 45
 Ser Ser Leu
 50

<210> 652
 <211> 151
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (131)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (145)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 652
 Asn Asn Lys His Tyr Leu Ser Phe Cys Gly Ser Gly Phe Cys Pro Val
 1 5 10 15
 Tyr Leu Gly Phe Thr Gly Leu Ala Ser His Gln Ala Val Lys Val Leu
 20 25 30
 Val Val Ala Val Ile Ile Pro Arg Gln Asp Arg Glu Arg Ile Cys Leu
 35 40 45
 Gln Ala Gln Val Gly Arg Ile His Leu Arg Gly Cys Trp Thr Gly Pro
 50 55 60
 Pro Phe Leu Asp Gly Tyr Trp Ser Glu Ala Phe Tyr Asn Thr Leu Ser
 65 70 75 80
 Arg Gly Pro Leu His Arg Ala Pro His His Met Ala Thr Gly Phe His
 85 90 95
 Gln Arg Glu Gln Trp Lys Glu Gln Glu Lys Gly Asp Gln Gly Arg His
 100 105 110
 Arg Ser Leu Leu Val Ala Ser Pro Gln Lys Arg Cys Tyr Phe Cys Cys
 115 120 125

379

Ile Leu Xaa Val Arg Ser Glu Ser Leu Gly Pro Gly Val Glu Phe Tyr
 130 135 140

Xaa Gly Val Asn Gly Arg Arg
 145 150

<210> 653
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 653
 Glu Arg Ile Cys Leu Gln Ala Gln Val Gly Arg Ile His Leu Arg Gly
 1 5 10 15

Cys Trp Thr Gly Pro Pro Phe Leu Asp Gly Tyr Trp Ser Glu Ala Phe
 20 25 30

<210> 654
 <211> 26
 <212> PRT
 <213> Homo sapiens

<400> 654
 Ser Asp Gly Ser Gln Leu Pro Cys Asp Glu Val Pro Tyr Gly Glu Ala
 1 5 10 15

His Val Thr Arg Tyr Cys Lys Lys Pro Leu
 20 25

<210> 655
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 655
 His Gln Arg Glu Gln Trp Lys Glu Gln Glu Lys Gly Asp Gln Gly Arg
 1 5 10 15

His Arg Ser Leu Leu Val Ala Ser Pro Gln Lys
 20 25

<210> 656
 <211> 263
 <212> DNA
 <213> Homo sapiens

<400> 656
 gcttcgtgtc caaccctctt gcccttcgcc tgtgtgacctg gagccagtcc caccacgctc 60
 gcgtttcctc ctgtagtgct cacaggtccc agcaccgatg gcattccctt tgccctgagt 120

380

ctgcagcggg tcccttttgt gcttccttcc cctcaggtag cctctctccc cctgggccac 180
 tcccgggggt gaggggggta ccccttccca gtgtttttta ttctgtggg gctcacccca 240
 aagtattaaa agtagctttg taa 263

<210> 657
 <211> 263
 <212> DNA
 <213> Homo sapiens

<400> 657
 gcttcgtgtc caaccctctt gcccttcgcc tgtgtgcctg gagccagtcc caccacgctc 60
 gcgtttcttc ctgtagtgct cacagggtccc agcaccgatg gcattccctt tgccctgagt 120
 ctgcagcggg tcccttttgt gcttccttcc cctcaggtag cctctctccc cctgggccac 180
 tcccgggggt gaggggggta ccccttccca gtgtttttta ttctgtggg gctcacccca 240
 aagtattaaa agtagctttg taa 263

<210> 658
 <211> 263
 <212> DNA
 <213> Homo sapiens

<400> 658
 gcttcgtgtc caaccctctt gcccttcgcc tgtgtgcctg gagccagtcc caccacgctc 60
 gcgtttcttc ctgtagtgct cacagggtccc agcaccgatg gcattccctt tgccctgagt 120
 ctgcagcggg tcccttttgt gcttccttcc cctcaggtag cctctctccc cctgggccac 180
 tcccgggggt gaggggggta ccccttccca gtgtttttta ttctgtggg gctcacccca 240
 aagtattaaa agtagctttg taa 263

<210> 659
 <211> 56
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (10)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 659
 Phe Arg Ile Asn Arg Leu Thr Ile Gly Xaa Ala Val Ala Met Thr Arg
 1 5 10 15

381

Gly Asn Gln Arg Glu Leu Ala Arg Gln Lys Asn Met Lys Lys Gln Ser
 20 25 30

Asp Ser Val Lys Gly Lys Arg Arg Asp Asp Gly Leu Ser Ala Ala Ala
 35 40 45

Arg Lys Gln Arg Asp Ser Glu Ile
 50 55

<210> 660

<211> 29

<212> PRT

<213> Homo sapiens

<400> 660

Ala Val Ala Met Thr Arg Gly Asn Gln Arg Glu Leu Ala Arg Gln Lys
 1 5 10 15

Asn Met Lys Lys Gln Ser Asp Ser Val Lys Gly Lys Arg
 20 25

<210> 661

<211> 110

<212> PRT

<213> Homo sapiens

<400> 661

Lys Ser Arg Ala Thr Arg Leu Arg Glu Ser Ala Glu Met Thr Gly Phe
 1 5 10 15

Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser Cys Ser Arg Ser
 20 25 30

Arg Lys Arg Gln Thr Arg Arg Arg Arg Asn Pro Ser Ser Phe Val Ala
 35 40 45

Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro Gly Ala Ser Pro
 50 55 60

Thr Thr Leu Ala Phe Pro Pro Val Val Leu Thr Gly Pro Ser Thr Asp
 65 70 75 80

Gly Ile Pro Phe Ala Leu Ser Leu Gln Arg Val Pro Phe Val Leu Pro
 85 90 95

Ser Pro Gln Val Ala Ser Leu Pro Leu Gly His Ser Arg Gly
 100 105 110

<210> 662

<211> 26

<212> PRT

<213> Homo sapiens

<400> 662

382

Leu Arg Glu Ser Ala Glu Met Thr Gly Phe Leu Leu Pro Pro Ala Ser
 1 5 10 15

Arg Gly Thr Arg Arg Ser Cys Ser Arg Ser
 20 25

<210> 663

<211> 30

<212> PRT

<213> Homo sapiens

<400> 663

Val Val Leu Thr Gly Pro Ser Thr Asp Gly Ile Pro Phe Ala Leu Ser
 1 5 10 15

Leu Gln Arg Val Pro Phe Val Leu Pro Ser Pro Gln Val Ala
 20 25 30

<210> 664

<211> 59

<212> PRT

<213> Homo sapiens

<400> 664

Leu Leu Ser Thr Ser His Leu Leu Thr Gln Ser Tyr Ser Phe Asn Lys
 1 5 10 15

Arg Ser His Ser Phe Ala Trp Lys Asn Ala His Cys Ile Leu Gln Ser
 20 25 30

Glu Asn Asn Glu Leu Gln Asn Ser Val Tyr Ile Tyr Val Cys Ile Tyr
 35 40 45

Val His Phe Ile Cys Thr Phe Leu Cys Asp Ile
 50 55

<210> 665

<211> 32

<212> PRT

<213> Homo sapiens

<400> 665

Lys Arg Ser His Ser Phe Ala Trp Lys Asn Ala His Cys Ile Leu Gln
 1 5 10 15

Ser Glu Asn Asn Glu Leu Gln Asn Ser Val Tyr Ile Tyr Val Cys Ile
 20 25 30

<210> 666

<211> 160

<212> DNA

383

<213> Homo sapiens

<400> 666

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tggtcactg tcttacaatc actgctgtgg aatcatgata ccacttttag ctctttgcat      60
cttccttcag tgtatttttg tttttcaaga ggaagtagat tttaactgga caactttgag      120
tactgacatc attgataaat aaactggctt gtggtttcaa      160

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<210> 667

<211> 292

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 667

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Leu Asp Glu Leu Met Ala His Leu Thr Glu Met Gln Ala Lys Val Ala      15
 1              5              10
Val Arg Ala Asp Ala Gly Lys Lys His Leu Pro Asp Lys Gln Asp His      30
          20              25              30
Lys Ala Ser Leu Asp Ser Met Leu Gly Gly Leu Glu Gln Glu Leu Gln      45
          35              40              45
Asp Leu Gly Ile Ala Thr Val Pro Lys Gly His Cys Ala Ser Cys Gln      60
          50              55              60
Lys Pro Ile Ala Gly Lys Val Ile His Ala Leu Gly Gln Ser Trp His      80
          65              70              75              80
Pro Glu His Phe Val Cys Thr His Cys Lys Glu Glu Ile Gly Ser Ser      95
          85              90              95
Pro Phe Phe Glu Arg Ser Gly Leu Xaa Tyr Cys Pro Asn Asp Tyr His      110
          100              105              110
Gln Leu Phe Ser Pro Arg Cys Ala Tyr Cys Ala Ala Pro Ile Leu Asp      125
          115              120              125
Lys Val Leu Thr Ala Met Asn Gln Thr Trp His Pro Glu His Phe Phe      140
          130              135              140
Cys Ser His Cys Gly Glu Val Phe Gly Ala Glu Gly Phe His Glu Lys      160
          145              150              155              160
Asp Lys Lys Pro Tyr Cys Arg Lys Asp Phe Leu Ala Met Phe Ser Pro      175
          165              170              175
Lys Cys Gly Gly Cys Asn Arg Pro Val Leu Glu Asn Tyr Leu Ser Ala      190
          180              185              190

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384

Met Asp Thr Val Trp His Pro Glu Cys Phe Val Cys Gly Asp Cys Phe
 195 200 205

Thr Ser Phe Ser Thr Gly Ser Phe Phe Glu Leu Asp Gly Arg Pro Phe
 210 215 220

Cys Glu Leu His Tyr His His Arg Arg Gly Thr Leu Cys His Gly Cys
 225 230 235 240

Gly Gln Pro Ile Thr Gly Arg Cys Ile Ser Ala Met Gly Tyr Lys Phe
 245 250 255

His Pro Glu His Phe Val Cys Ala Phe Cys Leu Thr Gln Leu Ser Lys
 260 265 270

Gly Ile Phe Arg Glu Gln Asn Asp Lys Thr Tyr Cys Gln Pro Cys Phe
 275 280 285

Asn Lys Leu Phe
 290

<210> 668
 <211> 43
 <212> PRT
 <213> Homo sapiens

<400> 668
 Lys Ala Ser Leu Asp Ser Met Leu Gly Gly Leu Glu Gln Glu Leu Gln
 1 5 10 15

Asp Leu Gly Ile Ala Thr Val Pro Lys Gly His Cys Ala Ser Cys Gln
 20 25 30

Lys Pro Ile Ala Gly Lys Val Ile His Ala Leu
 35 40

<210> 669
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 669
 Cys Pro Asn Asp Tyr His Gln Leu Phe Ser Pro Arg Cys Ala Tyr Cys
 1 5 10 15

Ala Ala Pro Ile Leu Asp Lys Val Leu Thr Ala Met Asn Gln Thr Trp
 20 25 30

His Pro Glu His Phe Phe Cys Ser His Cys Gly Glu Val Phe Gly Ala
 35 40 45

Glu Gly
 50

<210> 670

385

<211> 67
 <212> PRT
 <213> Homo sapiens

<400> 670
 Asp Lys Lys Pro Tyr Cys Arg Lys Asp Phe Leu Ala Met Phe Ser Pro
 1 5 10 15
 Lys Cys Gly Gly Cys Asn Arg Pro Val Leu Glu Asn Tyr Leu Ser Ala
 20 25 30
 Met Asp Thr Val Trp His Pro Glu Cys Phe Val Cys Gly Asp Cys Phe
 35 40 45
 Thr Ser Phe Ser Thr Gly Ser Phe Phe Glu Leu Asp Gly Arg Pro Phe
 50 55 60
 Cys Glu Leu
 65

<210> 671
 <211> 46
 <212> PRT
 <213> Homo sapiens

<400> 671
 Cys Gly Gln Pro Ile Thr Gly Arg Cys Ile Ser Ala Met Gly Tyr Lys
 1 5 10 15
 Phe His Pro Glu His Phe Val Cys Ala Phe Cys Leu Thr Gln Leu Ser
 20 25 30
 Lys Gly Ile Phe Arg Glu Gln Asn Asp Lys Thr Tyr Cys Gln
 35 40 45

<210> 672
 <211> 334
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (145)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 672
 His Lys Ser Leu Ala Gly Ala Xaa Val Tyr Thr Thr Asn Ile Gln Glu
 1 5 10 15
 Leu Asn Val Tyr Ser Glu Ala Gln Glu Pro Lys Glu Ser Pro Pro Pro
 20 25 30

386

Ser Lys Thr Ser Ala Ala Ala Gln Leu Asp Glu Leu Met Ala His Leu
 35 40 45
 Thr Glu Met Gln Ala Lys Val Ala Val Arg Ala Asp Ala Gly Lys Lys
 50 55 60
 His Leu Pro Asp Lys Gln Asp His Lys Ala Ser Leu Asp Ser Met Leu
 65 70 75 80
 Gly Gly Leu Glu Gln Glu Leu Gln Asp Leu Gly Ile Ala Thr Val Pro
 85 90 95
 Lys Gly His Cys Ala Ser Cys Gln Lys Pro Ile Ala Gly Lys Val Ile
 100 105 110
 His Ala Leu Gly Gln Ser Trp His Pro Glu His Phe Val Cys Thr His
 115 120 125
 Cys Lys Glu Glu Ile Gly Ser Ser Pro Phe Phe Glu Arg Ser Gly Leu
 130 135 140
 Xaa Tyr Cys Pro Asn Asp Tyr His Gln Leu Phe Ser Pro Arg Cys Ala
 145 150 155 160
 Tyr Cys Ala Ala Pro Ile Leu Asp Lys Val Leu Thr Ala Met Asn Gln
 165 170 175
 Thr Trp His Pro Glu His Phe Phe Cys Ser His Cys Gly Glu Val Phe
 180 185 190
 Gly Ala Glu Gly Phe His Glu Lys Asp Lys Lys Pro Tyr Cys Arg Lys
 195 200 205
 Asp Phe Leu Ala Met Phe Ser Pro Lys Cys Gly Gly Cys Asn Arg Pro
 210 215 220
 Val Leu Glu Asn Tyr Leu Ser Ala Met Asp Thr Val Trp His Pro Glu
 225 230 235 240
 Cys Phe Val Cys Gly Asp Cys Phe Thr Ser Phe Ser Thr Gly Ser Phe
 245 250 255
 Phe Glu Leu Asp Gly Arg Pro Phe Cys Glu Leu His Tyr His His Arg
 260 265 270
 Arg Gly Thr Leu Cys His Gly Cys Gly Gln Pro Ile Thr Gly Arg Cys
 275 280 285
 Ile Ser Ala Met Gly Tyr Lys Phe His Pro Glu His Phe Val Cys Ala
 290 295 300
 Phe Cys Leu Thr Gln Leu Ser Lys Gly Ile Phe Arg Glu Gln Asn Asp
 305 310 315 320
 Lys Thr Tyr Cys Gln Pro Cys Phe Asn Lys Leu Phe Pro Leu
 325 330

387

<210> 673
<211> 22
<212> PRT
<213> Homo sapiens

<400> 673
Asn Val Tyr Ser Glu Ala Gln Glu Pro Lys Glu Ser Pro Pro Pro Ser
1 5 10 15

Lys Thr Ser Ala Ala Ala
20

<210> 674
<211> 26
<212> PRT
<213> Homo sapiens

<400> 674
Asp Ser Met Leu Gly Gly Leu Glu Gln Glu Leu Gln Asp Leu Gly Ile
1 5 10 15

Ala Thr Val Pro Lys Gly His Cys Ala Ser
20 25

<210> 675
<211> 26
<212> PRT
<213> Homo sapiens

<400> 675
Tyr Leu Ser Ala Met Asp Thr Val Trp His Pro Glu Cys Phe Val Cys
1 5 10 15

Gly Asp Cys Phe Thr Ser Phe Ser Thr Gly
20 25

<210> 676
<211> 26
<212> PRT
<213> Homo sapiens

<400> 676
Arg Cys Ile Ser Ala Met Gly Tyr Lys Phe His Pro Glu His Phe Val
1 5 10 15

Cys Ala Phe Cys Leu Thr Gln Leu Ser Lys
20 25

<210> 677
<211> 127
<212> PRT
<213> Homo sapiens

388

<220>

<221> SITE

<222> (87)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 677

Pro	Thr	Arg	Pro	Val	Leu	Phe	Phe	Ser	Thr	Cys	Gln	Ser	Cys	Ser	Ser
1				5					10					15	

Arg	Pro	Val	Arg	Gln	Glu	His	Leu	Gly	Cys	Arg	Thr	Met	Glu	Glu	Leu
		20						25					30		

Asp	Ala	Leu	Leu	Glu	Glu	Leu	Glu	Arg	Ser	Thr	Leu	Gln	Asp	Ser	Asp
		35					40					45			

Glu	Tyr	Ser	Asn	Pro	Ala	Pro	Leu	Pro	Leu	Asp	Gln	His	Ser	Arg	Lys
	50					55				60					

Glu	Thr	Asn	Leu	Asp	Glu	Thr	Ser	Glu	Ile	Leu	Ser	Ile	Gln	Asp	Asn
65					70					75					80

Thr	Ser	Pro	Leu	Pro	Ala	Xaa	Ser	Cys	Ile	Leu	Pro	Ile	Ser	Arg	Ser
				85					90					95	

Ser	Met	Ser	Thr	Val	Lys	Pro	Lys	Ser	Gln	Arg	Asn	His	His	His	Leu
			100					105				110			

Leu	Lys	Arg	Gln	Gln	Leu	Leu	Ser	Trp	Met	Ser	Ser	Trp	Leu	Thr	
		115					120					125			

<210> 678

<211> 28

<212> PRT

<213> Homo sapiens

<400> 678

Pro	Val	Arg	Gln	Glu	His	Leu	Gly	Cys	Arg	Thr	Met	Glu	Glu	Leu	Asp
1				5					10					15	

Ala	Leu	Leu	Glu	Glu	Leu	Glu	Arg	Ser	Thr	Leu	Gln				
			20					25							

<210> 679

<211> 21

<212> PRT

<213> Homo sapiens

<400> 679

Ser	Cys	Ile	Leu	Pro	Ile	Ser	Arg	Ser	Ser	Met	Ser	Thr	Val	Lys	Pro
1				5					10					15	

Lys	Ser	Gln	Arg	Asn											
			20												

<210> 680

389

<211> 11
<212> PRT
<213> Homo sapiens

<400> 680
Trp His Pro Glu His Phe Val Cys Thr His Cys
1 5 10

<210> 681
<211> 6
<212> PRT
<213> Homo sapiens

<400> 681
Leu Phe Ser Pro Arg Cys
1 5

<210> 682
<211> 6
<212> PRT
<213> Homo sapiens

<400> 682
Pro Ile Leu Asp Lys Val
1 5

<210> 683
<211> 8
<212> PRT
<213> Homo sapiens

<400> 683
Thr Trp His Pro Glu His Phe Phe
1 5

<210> 684
<211> 7
<212> PRT
<213> Homo sapiens

<400> 684
Glu Gly Phe His Glu Lys Asp
1 5

<210> 685
<211> 13
<212> PRT
<213> Homo sapiens

<400> 685
Lys Phe His Pro Glu His Phe Val Cys Ala Phe Cys Leu
1 5 10

390

<210> 686
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 686
 Pro Ile Thr Gly Arg Cys Ile
 1 5

<210> 687
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 687
 His Pro Glu His Phe Val Cys
 1 5

<210> 688
 <211> 31
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (12)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 688
 Arg Ile Tyr Cys Ser Glu Asp Thr Phe Ser Pro Xaa Ala Glu Ser Gly
 1 5 10 15
 Val Ser Trp Gln Ser Ser Val Ser Gln Leu Tyr Gln Asp Tyr Glu
 20 25 30

<210> 689
 <211> 452
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (61)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 689
 Met Gly Ser Ser Gln Ser Val Glu Ile Pro Gly Gly Gly Thr Glu Gly
 1 5 10 15
 Tyr His Val Leu Arg Val Gln Glu Asn Ser Pro Gly His Arg Ala Gly
 20 25 30
 Leu Glu Pro Phe Phe Asp Phe Ile Val Ser Ile Asn Gly Ser Arg Leu
 35 40 45

391

Asn Lys Asp Asn Asp Thr Leu Lys Asp Leu Leu Lys Xaa Asn Val Glu
 50 55 60
 Lys Pro Val Lys Met Leu Ile Tyr Ser Ser Lys Thr Leu Glu Leu Arg
 65 70 75 80
 Glu Thr Ser Val Thr Pro Ser Asn Leu Trp Gly Gly Gln Gly Leu Leu
 85 90 95
 Gly Val Ser Ile Arg Phe Cys Ser Phe Asp Gly Ala Asn Glu Asn Val
 100 105 110
 Trp His Val Leu Glu Val Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly
 115 120 125
 Leu Arg Pro His Ser Asp Tyr Ile Ile Gly Ala Asp Thr Val Met Asn
 130 135 140
 Glu Ser Glu Asp Leu Phe Ser Leu Ile Glu Thr His Glu Ala Lys Pro
 145 150 155 160
 Leu Lys Leu Tyr Val Tyr Asn Thr Asp Thr Asp Asn Cys Arg Glu Val
 165 170 175
 Ile Ile Thr Pro Asn Ser Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys
 180 185 190
 Gly Ile Gly Tyr Gly Tyr Leu His Arg Ile Pro Thr Arg Pro Phe Glu
 195 200 205
 Glu Gly Lys Lys Ile Ser Leu Pro Gly Gln Met Ala Gly Thr Pro Ile
 210 215 220
 Thr Pro Leu Lys Asp Gly Phe Thr Glu Val Gln Leu Ser Ser Val Asn
 225 230 235 240
 Pro Pro Ser Leu Ser Pro Pro Gly Thr Thr Gly Ile Glu Gln Ser Leu
 245 250 255
 Thr Gly Leu Ser Ile Ser Ser Thr Pro Pro Ala Val Ser Ser Val Leu
 260 265 270
 Ser Thr Gly Val Pro Thr Val Pro Leu Leu Pro Pro Gln Val Asn Gln
 275 280 285
 Ser Leu Thr Ser Val Pro Pro Met Asn Pro Ala Thr Thr Leu Pro Gly
 290 295 300
 Leu Met Pro Leu Pro Ala Gly Leu Pro Asn Leu Pro Asn Leu Asn Leu
 305 310 315 320
 Asn Leu Pro Ala Pro His Ile Met Pro Gly Val Gly Leu Pro Glu Leu
 325 330 335
 Val Asn Pro Gly Leu Pro Pro Leu Pro Ser Met Pro Pro Arg Asn Leu
 340 345 350

392

Pro Gly Ile Ala Pro Leu Pro Leu Pro Ser Glu Phe Leu Pro Ser Phe
 355 360 365

Pro Leu Val Pro Glu Ser Ser Ser Ala Ala Ser Ser Gly Glu Leu Leu
 370 375 380

Ser Ser Leu Pro Pro Thr Ser Asn Ala Pro Ser Asp Pro Ala Thr Thr
 385 390 395 400

Thr Ala Lys Ala Asp Ala Ala Ser Ser Leu Thr Val Asp Val Thr Pro
 405 410 415

Pro Thr Ala Lys Ala Pro Thr Thr Val Glu Asp Arg Val Gly Asp Ser
 420 425 430

Thr Pro Val Ser Glu Lys Pro Val Ser Ala Ala Val Asp Ala Asn Ala
 435 440 445

Ser Glu Ser Pro
 450

<210> 690

<211> 109

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 690

Ser Val Glu Ile Pro Gly Gly Gly Thr Glu Gly Tyr His Val Leu Arg
 1 5 10 15

Val Gln Glu Asn Ser Pro Gly His Arg Ala Gly Leu Glu Pro Phe Phe
 20 25 30

Asp Phe Ile Val Ser Ile Asn Gly Ser Arg Leu Asn Lys Asp Asn Asp
 35 40 45

Thr Leu Lys Asp Leu Leu Lys Xaa Asn Val Glu Lys Pro Val Lys Met
 50 55 60

Leu Ile Tyr Ser Ser Lys Thr Leu Glu Leu Arg Glu Thr Ser Val Thr
 65 70 75 80

Pro Ser Asn Leu Trp Gly Gly Gln Gly Leu Leu Gly Val Ser Ile Arg
 85 90 95

Phe Cys Ser Phe Asp Gly Ala Asn Glu Asn Val Trp His
 100 105

<210> 691

<211> 145

<212> PRT

393

<213> Homo sapiens

<400> 691

Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro His Ser Asp
 1 5 10 15
 Tyr Ile Ile Gly Ala Asp Thr Val Met Asn Glu Ser Glu Asp Leu Phe
 20 25 30
 Ser Leu Ile Glu Thr His Glu Ala Lys Pro Leu Lys Leu Tyr Val Tyr
 35 40 45
 Asn Thr Asp Thr Asp Asn Cys Arg Glu Val Ile Ile Thr Pro Asn Ser
 50 55 60
 Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr
 65 70 75 80
 Leu His Arg Ile Pro Thr Arg Pro Phe Glu Glu Gly Lys Lys Ile Ser
 85 90 95
 Leu Pro Gly Gln Met Ala Gly Thr Pro Ile Thr Pro Leu Lys Asp Gly
 100 105 110
 Phe Thr Glu Val Gln Leu Ser Ser Val Asn Pro Pro Ser Leu Ser Pro
 115 120 125
 Pro Gly Thr Thr Gly Ile Glu Gln Ser Leu Thr Gly Leu Ser Ile Ser
 130 135 140
 Ser
 145

<210> 692

<211> 145

<212> PRT

<213> Homo sapiens

<400> 692

Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro His Ser Asp
 1 5 10 15
 Tyr Ile Ile Gly Ala Asp Thr Val Met Asn Glu Ser Glu Asp Leu Phe
 20 25 30
 Ser Leu Ile Glu Thr His Glu Ala Lys Pro Leu Lys Leu Tyr Val Tyr
 35 40 45
 Asn Thr Asp Thr Asp Asn Cys Arg Glu Val Ile Ile Thr Pro Asn Ser
 50 55 60
 Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr
 65 70 75 80
 Leu His Arg Ile Pro Thr Arg Pro Phe Glu Glu Gly Lys Lys Ile Ser
 85 90 95

394

Leu Pro Gly Gln Met Ala Gly Thr Pro Ile Thr Pro Leu Lys Asp Gly
 100 105 110

Phe Thr Glu Val Gln Leu Ser Ser Val Asn Pro Pro Ser Leu Ser Pro
 115 120 125

Pro Gly Thr Thr Gly Ile Glu Gln Ser Leu Thr Gly Leu Ser Ile Ser
 130 135 140

Ser
 145

<210> 693
 <211> 151
 <212> PRT
 <213> Homo sapiens

<400> 693

Arg Ile Pro Thr Arg Pro Phe Glu Glu Gly Lys Lys Ile Ser Leu Pro
 1 5 10 15

Gly Gln Met Ala Gly Thr Pro Ile Thr Pro Leu Lys Asp Gly Phe Thr
 20 25 30

Glu Val Gln Leu Ser Ser Val Asn Pro Pro Ser Leu Ser Pro Pro Gly
 35 40 45

Thr Thr Gly Ile Glu Gln Ser Leu Thr Gly Leu Ser Ile Ser Ser Thr
 50 55 60

Pro Pro Ala Val Ser Ser Val Leu Ser Thr Gly Val Pro Thr Val Pro
 65 70 75 80

Leu Leu Pro Pro Gln Val Asn Gln Ser Leu Thr Ser Val Pro Pro Met
 85 90 95

Asn Pro Ala Thr Thr Leu Pro Gly Leu Met Pro Leu Pro Ala Gly Leu
 100 105 110

Pro Asn Leu Pro Asn Leu Asn Leu Asn Leu Pro Ala Pro His Ile Met
 115 120 125

Pro Gly Val Gly Leu Pro Glu Leu Val Asn Pro Gly Leu Pro Pro Leu
 130 135 140

Pro Ser Met Pro Pro Arg Asn
 145 150

<210> 694
 <211> 109
 <212> PRT
 <213> Homo sapiens

<400> 694

Pro Gly Leu Pro Pro Leu Pro Ser Met Pro Pro Arg Asn Leu Pro Gly
 1 5 10 15

395

Ile Ala Pro Leu Pro Leu Pro Ser Glu Phe Leu Pro Ser Phe Pro Leu
20 25 30
Val Pro Glu Ser Ser Ser Ala Ala Ser Ser Gly Glu Leu Leu Ser Ser
35 40 45
Leu Pro Pro Thr Ser Asn Ala Pro Ser Asp Pro Ala Thr Thr Thr Ala
50 55 60
Lys Ala Asp Ala Ala Ser Ser Leu Thr Val Asp Val Thr Pro Pro Thr
65 70 75 80
Ala Lys Ala Pro Thr Thr Val Glu Asp Arg Val Gly Asp Ser Thr Pro
85 90 95
Val Ser Glu Lys Pro Val Ser Ala Ala Val Asp Ala Asn
100 105

<210> 695
<211> 22
<212> PRT
<213> Homo sapiens

<400> 695
Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr
1 5 10 15
Leu His Arg Ile Pro Thr
20

<210> 696
<211> 10
<212> PRT
<213> Homo sapiens

<400> 696
Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro
1 5 10

<210> 697
<211> 8
<212> PRT
<213> Homo sapiens

<400> 697
Trp Gly Gly Gln Gly Leu Leu Gly
1 5

<210> 698
<211> 27
<212> PRT
<213> Homo sapiens

396

<400> 698

Arg Asn Gly Ala Leu Leu Asp Lys Asn Phe Phe Asn Ala Asn Ser His
 1 5 10 15

Phe Pro Val Lys Gly Glu Arg Ile Arg Arg
 20 25

<210> 699

<211> 97

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (83)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 699

Arg Gly Ser Gly Phe Gly Trp Thr Ser Phe Pro Arg Pro Leu Pro Thr
 1 5 10 15

Glu Leu Thr Cys Pro Gly Phe His Arg Glu Arg Ala Phe Pro Pro Asp
 20 25 30

Gly Arg Val Arg Gly Val Arg Gly Trp Gly Ile Arg Arg Gly Cys Arg
 35 40 45

Ala Val Trp Gly Val Gly Ala Cys Gly Cys Ser Pro Gly Ser Ser Trp
 50 55 60

Arg Gly Ser Ala His Arg Ala Ser Gly Pro Ala Asp Leu Pro Val Ala
 65 70 75 80

Cys Arg Xaa Glu Gly Gly Ala Asp Ser Pro Ser Leu Leu Pro Ser Pro
 85 90 95

Pro

<210> 700

<211> 23

<212> PRT

<213> Homo sapiens

<400> 700

Ala Val Trp Gly Val Gly Ala Cys Gly Cys Ser Pro Gly Ser Ser Trp
 1 5 10 15

Arg Gly Ser Ala His Arg Ala
 20

<210> 701

<211> 77

<212> PRT

<213> Homo sapiens

397

<400> 701

Tyr Arg Pro Thr Met Glu Lys Met Lys Gln Val Val Thr Gln Thr Arg
1 5 10 15

Trp Met Arg Pro Asp Ala Lys Arg Ala Asn Arg Arg His Arg Arg Ile
20 25 30

Ser Gly Lys Ile Phe Ala Trp Asn Pro Leu Pro Lys Thr Arg Phe Ser
35 40 45

Arg Leu Leu Lys Ala Val Ser Glu Asn Thr Lys Arg Pro Glu Pro Ser
50 55 60

Arg Pro Pro Trp Met Val Ser His Ser Val Glu Ala Ser
65 70 75

<210> 702

<211> 27

<212> PRT

<213> Homo sapiens

<400> 702

Phe Ala Trp Asn Pro Leu Pro Lys Thr Arg Phe Ser Arg Leu Leu Lys
1 5 10 15

Ala Val Ser Glu Asn Thr Lys Arg Pro Glu Pro
20 25

<210> 703

<211> 93

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (29)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (30)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (31)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (32)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (33)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (36)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (38)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 703
 Ile Tyr Lys Val Phe Arg His Thr Ala Gly Leu Lys Pro Glu Val Ser
 1 5 10 15
 Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa
 20 25 30
 Xaa Xaa Xaa Xaa Xaa Xaa Trp Ile Phe Gly Val Leu His Val Val His
 35 40 45
 Ala Ser Val Val Thr Ala Tyr Leu Phe Thr Val Ser Asn Ala Phe Gln
 50 55 60
 Gly Met Phe Ile Phe Leu Phe Leu Cys Val Leu Ser Arg Lys Ile Gln
 65 70 75 80
 Glu Glu Tyr Tyr Arg Leu Phe Lys Asn Val Pro Cys Cys
 85 90

399

<210> 704

<211> 55

<212> PRT

<213> Homo sapiens

<400> 704

Trp Ile Phe Gly Val Leu His Val Val His Ala Ser Val Val Thr Ala
 1 5 10 15

Tyr Leu Phe Thr Val Ser Asn Ala Phe Gln Gly Met Phe Ile Phe Leu
 20 25 30

Phe Leu Cys Val Leu Ser Arg Lys Ile Gln Glu Glu Tyr Tyr Arg Leu
 35 40 45

Phe Lys Asn Val Pro Cys Cys
 50 55

<210> 705

<211> 26

<212> PRT

<213> Homo sapiens

<400> 705

Ile Tyr Lys Val Phe Arg His Thr Ala Gly Leu Lys Pro Glu Val Ser
 1 5 10 15

Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg
 20 25

<210> 706

<211> 66

<212> PRT

<213> Homo sapiens

<400> 706

Ile Ile Tyr Lys Val Phe Arg His Thr Ala Gly Leu Lys Pro Glu Val
 1 5 10 15

Ser Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg Gly Ala Leu Ala Leu
 20 25 30

Leu Phe Leu Leu Gly Thr Thr Trp Ile Phe Gly Val Leu His Val Val
 35 40 45

His Ala Ser Val Val Thr Ala Tyr Leu Phe Thr Val Ser Asn Ala Phe
 50 55 60

Gln Gly
 65

<210> 707

<211> 32

<212> PRT

<213> Homo sapiens

400

<400> 707

Glu Val Ser Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg Gly Ala Leu
1 5 10 15
Ala Leu Leu Phe Leu Leu Gly Thr Thr Trp Ile Phe Gly Val Leu His
20 25 30

<210> 708

<211> 86

<212> PRT

<213> Homo sapiens

<400> 708

Thr Thr Ile Leu Arg Thr Cys Thr Ile Val Cys Phe Tyr Tyr Trp Phe
1 5 10 15
Asn Gly Val Met Val Leu Leu Phe Phe Leu Asp Arg Asn Leu Leu Thr
20 25 30
Phe Asn Gln Ala Ser Ile Met Pro Phe Ser Asn Thr Asp Phe Leu His
35 40 45
Cys Leu Ser Phe Lys Lys Lys Leu Met Leu Leu Arg Tyr Ile Phe Tyr
50 55 60
Val Val Leu Thr Gly Pro Thr Leu Ser Leu Lys Gly Asp Glu Asn Gln
65 70 75 80
Ile Lys Asn Leu Phe Thr
85

<210> 709

<211> 23

<212> PRT

<213> Homo sapiens

<400> 709

Ile Val Cys Phe Tyr Tyr Trp Phe Asn Gly Val Met Val Leu Leu Phe
1 5 10 15
Phe Leu Asp Arg Asn Leu Leu
20

<210> 710

<211> 24

<212> PRT

<213> Homo sapiens

<400> 710

Leu Leu Arg Tyr Ile Phe Tyr Val Val Leu Thr Gly Pro Thr Leu Ser
1 5 10 15

401

Leu Lys Gly Asp Glu Asn Gln Ile
20

<210> 711
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 711
Ala Leu Thr Arg Ile Pro Pro Gly Asp Trp Val Ile Asn Val Thr Ala
1 5 10 15
Val Ser Phe Ala Gly Lys Thr Thr Ala Arg Phe Phe Xaa His Ser Ser
20 25 30
Pro Pro Ser Leu Gly Asp Gln Ala Arg Thr Asp Pro Gly His Gln Arg
35 40 45
Arg Asp
50

<210> 712
<211> 38
<212> PRT
<213> Homo sapiens

<400> 712
Ser Met Leu Leu Leu Phe Pro Leu Gln Glu Arg Pro Gln Gln Asp Ser
1 5 10 15
Phe Ile Arg Leu Leu Leu Ala Trp Gly Thr Arg Leu Glu Leu Thr Leu
20 25 30

Asp Ile Lys Gly Gly Ile
35

<210> 713
<211> 130
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (76)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (80)

402

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (98)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (113)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 713

Thr	Gly	Leu	Trp	Ala	Asp	Gly	Phe	Ser	Ser	His	Ile	Ile	Pro	Pro	Leu
1				5					10					15	

Met	Ser	Arg	Val	Ser	Ser	Ser	Leu	Val	Pro	Gln	Ala	Arg	Arg	Arg	Arg
			20					25					30		

Met	Lys	Glu	Ser	Cys	Cys	Gly	Leu	Ser	Cys	Lys	Gly	Asn	Ser	Ser	Asn
		35					40					45			

Ile	Asp	Tyr	Pro	Val	Thr	Gly	Arg	Asn	Ser	Cys	Glu	Arg	Ala	Pro	Leu
	50					55					60				

Cys	Ala	Phe	Ala	Leu	His	Phe	Gln	Glu	Arg	Thr	Xaa	Ile	Thr	Gly	Xaa
65					70					75					80

Gly	Glu	Asp	Pro	Gly	Pro	Phe	Gln	Ser	Xaa	Gly	Arg	Val	Thr	Ala	Ser
				85					90					95	

Arg	Xaa	Thr	Leu	Ala	Cys	Ser	His	Val	Ala	Met	Thr	Pro	Ala	Gly	Cys
			100					105					110		

Xaa	Gln	Ala	Leu	Gly	Thr	Pro	Ser	Ser	Tyr	Cys	Val	Arg	Lys	Ala	Pro
	115						120					125			

Arg	Ala
	130

<210> 714

<211> 28

<212> PRT

<213> Homo sapiens

<400> 714

Gln	Ala	Arg	Arg	Arg	Met	Lys	Glu	Ser	Cys	Cys	Gly	Leu	Ser	Cys
1					5			10					15	

Lys	Gly	Asn	Ser	Ser	Asn	Ile	Asp	Tyr	Pro	Val	Thr
		20					25				

403

<210> 715
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 715
 Leu Trp Arg Ser Ser Gly Val Glu Arg
 1 5

<210> 716
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 716
 Leu Gln Glu Val Asn Ile Thr Leu Pro Glu Asn Ser Val Trp Tyr Glu
 1 5 10 15
 Arg Tyr Lys Phe Asp Ile Pro Val Phe His Leu
 20 25

<210> 717
 <211> 110
 <212> PRT
 <213> Homo sapiens

<400> 717
 Met Gln Gly Ser Gly Ser Gln Phe Arg Ala Cys Leu Leu Cys Leu Cys
 1 5 10 15
 Phe Ser Cys Pro Cys Ser Pro Gly Gly Pro Arg Trp Asn Ser Arg Gln
 20 25 30
 Gly Gly Arg Arg Phe Pro Lys Thr Cys Arg Ala Ile Ser Gln Asn Leu
 35 40 45
 Val Phe Lys Tyr Lys Thr Phe Cys Pro Val Arg Tyr Met Gln Pro His
 50 55 60
 Arg Ser Ser Leu Cys Leu His Phe Thr Ser Tyr Val Phe Ile Leu Ser
 65 70 75 80
 Thr Trp Gly Ser Leu Arg Thr Tyr Ser Thr Asp Leu Lys Lys Lys Lys
 85 90 95
 Lys Asn Ser Arg Gly Gly Pro Val Pro Ile Arg Pro Lys Ser
 100 105 110

<210> 718
 <211> 99
 <212> DNA
 <213> Homo sapiens

<220>

404

<221> SITE

<222> (24)

<223> n equals a,t,g, or c

<400> 718

tagcatgtag ccagtcgaat aacntataag gacaaagtgg agtccacgcg tgcggccgctc 60

tagactagtg gatcccccggtg ctgcaggatt cggcacgag 99

<210> 719

<211> 51

<212> PRT

<213> Homo sapiens

<400> 719

Met	Gln	Gly	Ser	Gly	Ser	Gln	Phe	Arg	Ala	Cys	Leu	Leu	Cys	Leu	Cys
1				5				10					15		

Phe	Ser	Cys	Pro	Cys	Ser	Pro	Gly	Gly	Pro	Arg	Trp	Asn	Ser	Arg	Gln
		20					25					30			

Gly	Gly	Arg	Arg	Phe	Pro	Lys	Thr	Cys	Arg	Ala	Ile	Ser	Gln	Asn	Leu
		35					40					45			

Val	Phe	Lys
	50	

<210> 720

<211> 54

<212> PRT

<213> Homo sapiens

<400> 720

Pro	Val	Arg	Tyr	Met	Gln	Pro	His	Arg	Ser	Ser	Leu	Cys	Leu	His	Phe
1				5				10					15		

Thr	Ser	Tyr	Val	Phe	Ile	Leu	Ser	Thr	Trp	Gly	Ser	Leu	Arg	Thr	Tyr
		20					25					30			

Ser	Thr	Asp	Leu	Lys	Lys	Lys	Lys	Lys	Asn	Ser	Arg	Gly	Gly	Pro	Val
		35					40					45			

Pro	Ile	Arg	Pro	Lys	Ser
	50				

<210> 721

<211> 38

<212> PRT

<213> Homo sapiens

<400> 721

Gly	Glu	Glu	Gln	Arg	Asp	Cys	Ser	Leu	Gly	Trp	Arg	Gly	Val	Gly	Met
1				5					10				15		

405

Arg Ala Thr His Cys Gln Ala Ala Arg Met Phe Val Leu Phe Ser Leu
 20 25 30

Pro Lys Tyr Ala Gly Leu
 35

<210> 722

<211> 39

<212> PRT

<213> Homo sapiens

<400> 722

Thr Ser Gly Ser Pro Gly Cys Arg Ile Arg His Glu Leu Pro Gly Glu
 1 5 10 15

Glu Gln Arg Asp Cys Ser Leu Gly Trp Arg Gly Val Gly Met Arg Ala
 20 25 30

Thr His Cys Gln Ala Ala Arg
 35

<210> 723

<211> 128

<212> PRT

<213> Homo sapiens

<400> 723

Glu Pro Pro Ile Ala Lys Gln Gln Glu Cys Ser Cys Phe Phe Pro Phe
 1 5 10 15

Gln Asn Met Gln Gly Ser Gly Ser Gln Phe Arg Ala Cys Leu Leu Cys
 20 25 30

Leu Cys Phe Ser Cys Pro Cys Ser Pro Gly Gly Pro Arg Trp Asn Ser
 35 40 45

Arg Gln Gly Gly Arg Arg Phe Pro Lys Thr Cys Arg Ala Ile Ser Gln
 50 55 60

Asn Leu Val Phe Lys Tyr Lys Thr Phe Cys Pro Val Arg Tyr Met Gln
 65 70 75 80

Pro His Arg Ser Ser Leu Cys Leu His Phe Thr Ser Tyr Val Phe Ile
 85 90 95

Leu Ser Thr Trp Gly Ser Leu Arg Thr Tyr Ser Thr Asp Leu Lys Lys
 100 105 110

Lys Lys Lys Asn Ser Arg Gly Gly Pro Val Pro Ile Arg Pro Lys Ser
 115 120 125

<210> 724

406

<211> 31
 <212> PRT
 <213> Homo sapiens

<400> 724
 Gln Phe Arg Ala Cys Leu Leu Cys Leu Cys Phe Ser Cys Pro Cys Ser
 1 5 10 15
 Pro Gly Gly Pro Arg Trp Asn Ser Arg Gln Gly Gly Arg Arg Phe
 20 25 30

<210> 725
 <211> 23
 <212> PRT
 <213> Homo sapiens

<400> 725
 Asn Gln Phe Thr Ser Cys Ile Leu Phe Cys Asp Gly Gly His Trp Arg
 1 5 10 15
 Glu Leu Leu Phe Gln Ser Ile
 20

<210> 726
 <211> 101
 <212> PRT
 <213> Homo sapiens

<400> 726
 Ala Met Ser Ser Lys Leu Leu Asn Leu Leu Ala Leu Leu Gln Tyr Ser
 1 5 10 15
 Val His Asp His Cys His Pro Arg Arg Leu Leu Lys Arg Gly Ala Arg
 20 25 30
 Ala Thr Leu Arg His Lys Gly Trp Gly Pro Ser Ser Leu Arg Gly Cys
 35 40 45
 Glu Ser Phe Gln Ile Val Leu Ile Gly Trp Gly Pro Asp Leu Ala Val
 50 55 60
 Gly Phe Gly Arg Gly Lys Leu Leu Ser Arg Ser Leu Pro Val Arg His
 65 70 75 80
 Gly Gly Val Ser Glu Phe Cys Leu Pro His Arg Asp Val Val Arg Leu
 85 90 95
 Glu Lys Val Lys Lys
 100

<210> 727
 <211> 33
 <212> PRT
 <213> Homo sapiens

407

<400> 727

Gly Pro Ser Ser Leu Arg Gly Cys Glu Ser Phe Gln Ile Val Leu Ile
 1 5 10 15

Gly Trp Gly Pro Asp Leu Ala Val Gly Phe Gly Arg Gly Lys Leu Leu
 20 25 30

Ser

<210> 728

<211> 32

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 728

Thr Arg Lys Asn Ile Asp Phe Xaa Glu Thr Glu Lys Tyr Tyr Leu Phe
 1 5 10 15

Ser Phe Ser Asn Asn Val Ser Phe Lys Asn Phe Trp Leu Lys Tyr Asn
 20 25 30

<210> 729

<211> 161

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (46)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 729

Met Pro Arg Lys Thr Ser Lys Cys Arg Gln Leu Leu Cys Ser Gly Ala
 1 5 10 15

Ser Arg Asn Ala Asp Thr Ala Ala Arg Gln Ser Thr Cys Ser Ser His
 20 25 30

Arg Pro Pro Gly Lys Ile Pro Ser Leu Gly Pro Arg Arg Xaa Pro Gly
 35 40 45

Cys Xaa Ser Val Pro Ser Ser Arg Gly Glu Gln Ser Thr Gly Ser Pro

408

50 55 60
 Ala Ala Pro Arg Cys Gly Arg Arg Asp Ala His Arg Gly Leu Pro Gly
 65 70 75 80
 Gly Ala Ala Met Thr Pro Gly Asp Thr Trp Ala Ser Phe Asn Pro Arg
 85 90 95
 Ala Gly His Ser Lys Ser Gln Gly Glu Gly Gln Glu Ser Ser Gly Ala
 100 105 110
 Ser Arg Gln Asp Arg His Pro Val Ser His Trp Val Glu Arg Gln Arg
 115 120 125
 Glu Ala Trp Gly Ala Pro Arg Ser Ser Ser Ala Gly Gly Val Lys Val
 130 135 140
 Ala Ala Thr Thr Glu Arg Glu Pro Glu Phe Lys Ile Lys Thr Gly Lys
 145 150 155 160

Ala

<210> 730

<211> 88

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 730

Cys Ser Gly Ala Ser Arg Asn Ala Asp Thr Ala Ala Arg Gln Ser Thr
 1 5 10 15

Cys Ser Ser His Arg Pro Pro Gly Lys Ile Pro Ser Leu Gly Pro Arg
 20 25 30

Arg Xaa Pro Gly Cys Xaa Ser Val Pro Ser Ser Arg Gly Glu Gln Ser
 35 40 45

Thr Gly Ser Pro Ala Ala Pro Arg Cys Gly Arg Arg Asp Ala His Arg
 50 55 60

Gly Leu Pro Gly Gly Ala Ala Met Thr Pro Gly Asp Thr Trp Ala Ser
 65 70 75 80

Phe Asn Pro Arg Ala Gly His Ser
 85

409

<210> 731
 <211> 59
 <212> PRT
 <213> Homo sapiens

<400> 731
 Gln Gly Glu Gly Gln Glu Ser Ser Gly Ala Ser Arg Gln Asp Arg His
 1 5 10 15
 Pro Val Ser His Trp Val Glu Arg Gln Arg Glu Ala Trp Gly Ala Pro
 20 25 30
 Arg Ser Ser Ser Ala Gly Gly Val Lys Val Ala Ala Thr Thr Glu Arg
 35 40 45
 Glu Pro Glu Phe Lys Ile Lys Thr Gly Lys Ala
 50 55

<210> 732
 <211> 63
 <212> PRT
 <213> Homo sapiens

<400> 732
 Ile Arg His Glu Gly Lys Arg Met Leu Asn Glu Ser Arg Lys Pro Leu
 1 5 10 15
 Ser Phe Ala Ser Arg Leu Ser Ser Leu Tyr Phe Lys Leu Gly Phe Pro
 20 25 30
 Phe Cys Gly Arg Ser Asn Leu Tyr Ser Thr Cys Thr Ala Ala Pro Gly
 35 40 45
 Gly Ser Pro Gly Leu Pro Leu Pro Phe Tyr Pro Val Ala Asp Gly
 50 55 60

<210> 733
 <211> 176
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (127)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 733
 Thr Arg Ala Glu Ser Leu Phe Pro Leu Leu His Ala Phe Pro Val Phe
 1 5 10 15
 Ile Leu Asn Ser Gly Ser Leu Ser Val Val Ala Ala Thr Phe Thr Pro
 20 25 30
 Pro Ala Leu Leu Leu Leu Gly Ala Pro Gln Ala Ser Leu Cys Leu Ser
 35 40 45

410

Thr Gln Trp Leu Thr Gly Cys Leu Ser Cys Leu Asp Ala Pro Leu Leu
 50 55 60
 Ser Cys Pro Ser Pro Trp Leu Leu Leu Cys Pro Ala Leu Gly Leu Lys
 65 70 75 80
 Leu Ala His Val Ser Pro Gly Val Met Ala Ala Pro Pro Gly Arg Pro
 85 90 95
 Leu Cys Ala Ser Arg Leu Pro His Leu Gly Ala Ala Gly Glu Pro Val
 100 105 110
 Leu Cys Ser Pro Arg Leu Leu Gly Thr Glu Leu Gln Pro Gly Xaa Leu
 115 120 125
 Arg Gly Pro Arg Leu Gly Ile Leu Pro Gly Gly Arg Trp Glu Glu Gln
 130 135 140
 Val Leu Cys Leu Ala Ala Val Ser Ala Phe Leu Asp Ala Pro Glu His
 145 150 155 160
 Arg Ser Cys Arg His Phe Glu Val Phe Leu Gly Met Cys Gln Ile Thr
 165 170 175

<210> 734
 <211> 29
 <212> PRT
 <213> Homo sapiens

<400> 734
 Pro Ala Leu Gly Leu Lys Leu Ala His Val Ser Pro Gly Val Met Ala
 1 5 10 15
 Ala Pro Pro Gly Arg Pro Leu Cys Ala Ser Arg Leu Pro
 20 25

<210> 735
 <211> 24
 <212> PRT
 <213> Homo sapiens

<400> 735
 Gly Gly Arg Trp Glu Glu Gln Val Leu Cys Leu Ala Ala Val Ser Ala
 1 5 10 15
 Phe Leu Asp Ala Pro Glu His Arg
 20

<210> 736
 <211> 98
 <212> PRT

411

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 736

Ser Trp Pro Met Cys Pro Pro Glu Ser Trp Leu Leu Leu Leu Gly Gly
 1 5 10 15
 Leu Cys Val Arg His Val Phe His Thr Trp Gly Gln Leu Ala Ser Pro
 20 25 30
 Cys Ser Val Pro Leu Gly Cys Leu Ala Gln Ser Cys Ser Leu Gly Xaa
 35 40 45
 Ser Val Asp Pro Asp Trp Gly Phe Cys Gln Gly Gly Asp Gly Arg Ser
 50 55 60
 Arg Cys Phe Ala Trp Arg Leu Cys Leu His Phe Trp Thr Pro Gln Ser
 65 70 75 80
 Thr Glu Val Ala Gly Thr Leu Arg Ser Ser Ser Ala Cys Ala Arg Leu
 85 90 95
 His Glu

<210> 737

<211> 29

<212> PRT

<213> Homo sapiens

<400> 737

Gly Asp Gly Arg Ser Arg Cys Phe Ala Trp Arg Leu Cys Leu His Phe
 1 5 10 15
 Trp Thr Pro Gln Ser Thr Glu Val Ala Gly Thr Leu Arg
 20 25

<210> 738

<211> 235

<212> PRT

<213> Homo sapiens

<400> 738

Met Ser Pro Arg Tyr Pro Gly Gly Pro Arg Pro Pro Leu Arg Ile Pro
 1 5 10 15
 Asn Gln Ala Leu Gly Gly Val Pro Gly Ser Gln Pro Leu Leu Pro Ser
 20 25 30
 Gly Met Asp Pro Thr Arg Gln Gln Gly His Pro Asn Met Gly Gly Pro
 35 40 45

412

Met Gln Arg Met Thr Pro Pro Arg Gly Met Val Pro Leu Gly Pro Gln
 50 55 60

Asn Tyr Gly Gly Ala Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro
 65 70 75 80

Gly Met Pro Gly Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro
 85 90 95

Asn Pro Thr Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly
 100 105 110

Asn Tyr Val Gly Pro Pro Gly Gly Gly Gly Pro Pro Gly Thr Pro Ile
 115 120 125

Met Pro Ser Pro Ala Asp Ser Thr Asn Ser Gly Asp Asn Met Tyr Thr
 130 135 140

Leu Met Asn Ala Val Pro Pro Gly Pro Asn Arg Pro Asn Phe Pro Met
 145 150 155 160

Gly Pro Gly Ser Asp Gly Pro Met Gly Gly Leu Gly Gly Met Glu Ser
 165 170 175

His His Met Asn Gly Ser Leu Gly Ser Gly Asp Met Asp Ser Ile Ser
 180 185 190

Lys Asn Ser Pro Asn Asn Met Ser Leu Ser Asn Gln Pro Gly Thr Pro
 195 200 205

Arg Asp Asp Gly Glu Met Gly Gly Asn Phe Leu Asn Pro Phe Gln Ser
 210 215 220

Glu Ser Tyr Ser Pro Ser Met Thr Met Ser Val
 225 230 235

<210> 739

<211> 114

<212> PRT

<213> Homo sapiens

<400> 739

Met Ser Pro Arg Tyr Pro Gly Gly Pro Arg Pro Pro Leu Arg Ile Pro
 1 5 10 15

Asn Gln Ala Leu Gly Gly Val Pro Gly Ser Gln Pro Leu Leu Pro Ser
 20 25 30

Gly Met Asp Pro Thr Arg Gln Gln Gly His Pro Asn Met Gly Gly Pro
 35 40 45

Met Gln Arg Met Thr Pro Pro Arg Gly Met Val Pro Leu Gly Pro Gln
 50 55 60

Asn Tyr Gly Gly Ala Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro
 65 70 75 80

Gly Met Pro Gly Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro
85 90 95

Asn Pro Thr Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly
100 105 110

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<210> 740
<211> 81
<212> PRT
<213> Homo sapiens
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<400> 740
Leu Asn Ala Leu Gly Gly Pro Gly Met Pro Gly Met Asn Met Gly Pro
1 5 10 15

Gly Gly Gly Arg Pro Trp Pro Asn Pro Thr Asn Ala Asn Ser Ile Pro
20 25 30

Tyr Ser Ser Ala Ser Pro Gly Asn Tyr Val Gly Pro Pro Gly Gly Gly
35 40 45

Gly Pro Pro Gly Thr Pro Ile Met Pro Ser Pro Ala Asp Ser Thr Asn
50 55 60

Ser Gly Asp Asn Met Tyr Thr Leu Met Asn Ala Val Pro Pro Gly Pro
65 70 75 80

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<210> 741
<211> 70
<212> PRT
<213> Homo sapiens
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<400> 741
Gly Pro Met Gly Gly Leu Gly Gly Met Glu Ser His His Met Asn Gly
1 5 10 15

Ser Leu Gly Ser Gly Asp Met Asp Ser Ile Ser Lys Asn Ser Pro Asn
20 25 30

Asn Met Ser Leu Ser Asn Gln Pro Gly Thr Pro Arg Asp Asp Gly Glu
35 40 45

Met Gly Gly Asn Phe Leu Asn Pro Phe Gln Ser Glu Ser Tyr Ser Pro
50 55 60

Ser Met Thr Met Ser Val
65 70

<210> 742

414

<211> 14
 <212> PRT
 <213> Homo sapiens

<400> 742
 Thr Cys Glu His Ser Ser Glu Ala Lys Ala Phe His Asp Tyr
 1 5 10

<210> 743
 <211> 19
 <212> PRT
 <213> Homo sapiens

<400> 743
 Arg Arg Glu Thr Cys Glu His Ser Ser Glu Ala Lys Ala Phe His Asp
 1 5 10 15

Tyr Pro Phe

<210> 744
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 744
 Thr Ile Thr Leu Phe Gln Ser Ala Trp Cys Phe Phe Ser Lys Tyr Cys
 1 5 10 15

Thr Asp Phe Thr
 20

<210> 745
 <211> 105
 <212> PRT
 <213> Homo sapiens

<400> 745
 Val Arg Gly Cys Glu Asp Gly Gly Gly Gly Gly Ile Trp Gly Gly Trp
 1 5 10 15

Trp Pro Gly Gln Gln Met Ala Pro Pro Trp Leu Ser Cys Pro His Arg
 20 25 30

Gln Phe Pro His Phe His Ser Gly Arg Gln Arg Arg Gln Ser Asp Leu
 35 40 45

Leu Lys Glu Glu Leu Pro Gln Pro Ser Gly Ala Ala Gly Arg Ala Ser
 50 55 60

Gly Asn Lys Pro Tyr Thr Pro Pro Pro Ala Ser Asn Ser Leu Thr Leu
 65 70 75 80

Arg Leu Leu Ser Phe Arg Phe Asn Ala Phe Asn Arg Ser His Pro Gln
 85 90 95

415

Pro Ser Leu Asn Tyr Lys Asp Arg Gln
 100 105

<210> 746
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 746
 Pro Trp Leu Ser Cys Pro His Arg Gln Phe Pro His Phe His Ser Gly
 1 5 10 15

Arg Gln Arg Arg Gln Ser Asp Leu Leu
 20 25

<210> 747
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 747
 Arg Leu Leu Ser Phe Arg Phe Asn Ala Phe Asn Arg Ser His Pro Gln
 1 5 10 15

Pro Ser Leu Asn
 20

<210> 748
 <211> 56
 <212> PRT
 <213> Homo sapiens

<400> 748
 Arg Asp Ser Ser Leu Trp Ala Ala Ala Leu Ser Phe Arg Gln Gln Cys
 1 5 10 15

Ser Ser Leu Ala Ser Cys Leu Val Ser Met Tyr Ser Arg Pro Gly Arg
 20 25 30

Gln His Arg Ala Lys Ala Gly Ala Gly Ser Gln Thr Glu Gln Cys Trp
 35 40 45

Gly Arg Lys Val Asp Ala Val Val
 50 55

<210> 749
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 749
 Cys Leu Val Ser Met Tyr Ser Arg Pro Gly Arg Gln His Arg Ala Lys
 1 5 10 15

416

Ala Gly Ala Gly Ser Gln Thr Glu Gln Cys Trp
 20 25

<210> 750

<211> 86

<212> PRT

<213> Homo sapiens

<400> 750

Pro Glu His Gly Phe Ser Ser Cys Asp Phe Trp Glu Gly Ala Pro Ser
 1 5 10 15

Ser Gly Pro Lys Glu Gly Gly Arg Ser Pro Pro Gln Leu Ala Cys Val
 20 25 30

Trp Gly Met Asn Leu Ser Ser Pro Pro Cys Leu Ala Leu Leu Thr Asn
 35 40 45

Arg Ala Cys Leu Ala Val Asn Trp His Arg Val Thr Leu Phe Pro Gly
 50 55 60

Ile Gln Val Cys Asn Gln Asn Thr Gly Glu Glu Lys Leu Gln Asp Pro
 65 70 75 80

Cys Pro His Leu Ser Ser
 85

<210> 751

<211> 30

<212> PRT

<213> Homo sapiens

<400> 751

Arg Ser Pro Pro Gln Leu Ala Cys Val Trp Gly Met Asn Leu Ser Ser
 1 5 10 15

Pro Pro Cys Leu Ala Leu Leu Thr Asn Arg Ala Cys Leu Ala
 20 25 30

<210> 752

<211> 74

<212> PRT

<213> Homo sapiens

<400> 752

Cys Glu Arg Asp Ser Glu Thr Ser Ser Ile Ala Met Thr Cys Ile Lys
 1 5 10 15

His Lys Pro Pro Lys Gln Lys Lys Arg Leu Ser Leu Leu Pro Gly Phe
 20 25 30

Arg Ser Ala Leu Pro Arg Val Cys Arg Cys His Met Ile Thr Val Gln
 35 40 45

417

Arg Glu Ala Phe Arg Thr His Thr Gly Cys Ser Thr Ser Val His Leu
 50 55 60

Pro Ser Arg Gly Gly Phe Leu Pro Asp Phe
 65 70

<210> 753
 <211> 28
 <212> PRT
 <213> Homo sapiens

<400> 753
 Lys Lys Arg Leu Ser Leu Leu Pro Gly Phe Arg Ser Ala Leu Pro Arg
 1 5 10 15

Val Cys Arg Cys His Met Ile Thr Val Gln Arg Glu
 20 25

<210> 754
 <211> 59
 <212> PRT
 <213> Homo sapiens

<400> 754
 Gln Ala Phe Val Leu Leu Ser Asp Leu Leu Leu Ile Phe Ser Pro Gln
 1 5 10 15

Met Ile Val Gly Gly Arg Asp Phe Leu Arg Pro Leu Val Phe Phe Pro
 20 25 30

Glu Ala Thr Leu Gln Ser Glu Leu Ala Ser Phe Leu Met Asp His Val
 35 40 45

Phe Ile Gln Pro Gly Asp Leu Gly Ser Gly Ala
 50 55

<210> 755
 <211> 43
 <212> PRT
 <213> Homo sapiens

<400> 755
 Ala Cys Ser Tyr Leu Leu Cys Asn Pro Glu Phe Thr Phe Phe Ser Arg
 1 5 10 15

Ala Asp Phe Ala Arg Ser Gln Leu Val Asp Leu Leu Thr Asp Arg Phe
 20 25 30

Gln Gln Glu Leu Glu Glu Leu Leu Gln Val Gly
 35 40

<210> 756
 <211> 35
 <212> PRT

418

<213> Homo sapiens

<400> 756

Gln Lys Gln Leu Ser Ser Leu Arg Asp Arg Met Val Ala Phe Cys Glu
 1 5 10 15

Leu Cys Gln Ser Cys Leu Ser Asp Val Asp Thr Glu Ile Gln Glu Gln
 20 25 30

Val Ser Thr
 35

<210> 757

<211> 27

<212> PRT

<213> Homo sapiens

<400> 757

Gln Val Ile Leu Pro Ala Leu Thr Leu Val Tyr Phe Ser Ile Leu Trp
 1 5 10 15

Thr Leu Thr His Ile Ser Lys Ser Asp Ala Ser
 20 25

<210> 758

<211> 31

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (26)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 758

Ser Thr His Asp Leu Thr Arg Trp Glu Leu Tyr Glu Pro Cys Cys Gln
 1 5 10 15

Leu Leu Gln Lys Ala Val Asp Thr Gly Xaa Val Pro His Gln Val
 20 25 30

<210> 759

<211> 66

<212> PRT

<213> Homo sapiens

<400> 759

Thr Ser Phe Leu Phe Pro Leu Gln Ala Phe Val Leu Leu Ser Asp Leu
 1 5 10 15

Leu Leu Ile Phe Ser Pro Gln Met Ile Val Gly Gly Arg Asp Phe Leu
 20 25 30

Arg Pro Leu Val Phe Phe Pro Glu Ala Thr Leu Gln Ser Glu Leu Ala
 35 40 45

419

Ser Phe Leu Met Asp His Val Phe Ile Gln Pro Gly Asp Leu Gly Ser
 50 55 60

Gly Ala
 65

<210> 760

<211> 68

<212> PRT

<213> Homo sapiens

<400> 760

Gly Trp Gly Ala Cys Ser Tyr Leu Leu Cys Asn Pro Glu Phe Thr Phe
 1 5 10 15

Phe Ser Arg Ala Asp Phe Ala Arg Ser Gln Leu Val Asp Leu Leu Thr
 20 25 30

Asp Arg Phe Gln Gln Glu Leu Glu Glu Leu Leu Gln Val Gly Ala Gly
 35 40 45

Ala Gly Gln Trp Asp Thr Pro Asn Lys Gly Gly Arg Gly Cys Lys Thr
 50 55 60

Gly Asp Val Asp
 65

<210> 761

<211> 78

<212> PRT

<213> Homo sapiens

<400> 761

Val Trp Val Leu Asp Gly Ile Met Gly Thr Glu Glu Ser Val Ser Ser
 1 5 10 15

Phe Phe Pro Phe Lys Pro Leu Cys Pro Gln Lys Gln Leu Ser Ser Leu
 20 25 30

Arg Asp Arg Met Val Ala Phe Cys Glu Leu Cys Gln Ser Cys Leu Ser
 35 40 45

Asp Val Asp Thr Glu Ile Gln Glu Gln Val Ser Thr Asp Ser Ser Gly
 50 55 60

Ser Asn Lys Ala Ser Ile Pro Ala Pro Ile Pro Arg Arg Asn
 65 70 75

<210> 762

<211> 152

<212> PRT

<213> Homo sapiens

<220>

420

<221> SITE

<222> (67)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (86)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 762

Asn Ala Ser Leu Pro Ser Thr Ser Glu Trp Leu Ser Ser Ser Ser Pro
 1 5 10 15

Ser Arg Phe Tyr Trp Cys Leu Trp Ser Trp Phe Pro Leu Phe Phe Ser
 20 25 30

Ser Ile Thr Phe Pro Phe Leu Pro Gln Ser Thr His Asp Leu Thr Arg
 35 40 45

Trp Glu Leu Tyr Glu Pro Cys Cys Gln Leu Leu Gln Lys Ala Val Asp
 50 55 60

Thr Gly Xaa Val Pro His Gln Val Ser Gly Gln Ala Arg Asp Gly Leu
 65 70 75 80

Gly Ala Gly Gly Leu Xaa Phe Lys Asp Leu Arg Ser Arg Trp Pro Leu
 85 90 95

Gly Val Ser Ser Leu Ser Ala Trp Ser Gly Gln Ser Glu Glu Asp Gln
 100 105 110

Val Gly Gly Gly His Leu Leu His Ser Ser Leu Arg Arg Trp Thr Leu
 115 120 125

Leu Pro Gly Ser Ser Trp Ile Ser Trp Lys Pro Arg Ile Ile Leu Arg
 130 135 140

Asp Ser Arg Arg Arg Arg Val Asn
 145 150

<210> 763

<211> 38

<212> PRT

<213> Homo sapiens

<400> 763

Val Leu Gly Glu Met Leu Leu Trp Ile Phe Phe Pro Ser Gln Ser Ser
 1 5 10 15

Phe Leu Asp Glu Asp Glu Val Tyr Asn Leu Ala Ala Thr Leu Lys Arg
 20 25 30

Leu Ser Ala Phe Tyr Lys
 35

<210> 764

421

<211> 44
 <212> PRT
 <213> Homo sapiens

<400> 764
 Pro Lys Pro His Phe Ser Asn Pro Leu Leu Leu Gln Val Ile Leu Pro
 1 5 10 15

Ala Leu Thr Leu Val Tyr Phe Ser Ile Leu Trp Thr Leu Thr His Ile
 20 25 30

Ser Lys Ser Asp Ala Ser Pro Gly Glu Cys Gly Ser
 35 40

<210> 765
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 765
 His Cys Gln Phe Leu Leu Gly
 1 5

<210> 766
 <211> 53
 <212> PRT
 <213> Homo sapiens

<400> 766
 Glu Phe Gly Thr Ser Leu Val Ala Leu Glu Leu His Glu Leu Leu Tyr
 1 5 10 15

His Trp Glu Thr Arg Ala Gln Pro Ser Leu Ile Leu Tyr Val Val Ser
 20 25 30

Asp Leu Arg Trp Met Glu Phe Arg Thr Ser Cys Leu Leu Phe Asp Phe
 35 40 45

Val Leu Phe Leu Glu
 50

<210> 767
 <211> 54
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 767
 Thr Lys Pro Gly Met Val Gly His Val Pro Ile Val Pro Ala Thr Lys
 1 5 10 15

422

Xaa Ala Glu Ala Gly Gly Ser Pro Glu Pro Gly Ser Ser Thr Leu Gln
 20 25 30

Trp Pro Met Ile Thr Pro Cys Thr Pro Ser Trp Ala Thr Glu Pro Asp
 35 40 45

His Val Ser Glu Asp Glu
 50

<210> 768

<211> 30

<212> PRT

<213> Homo sapiens

<400> 768

Leu Leu Tyr His Trp Glu Thr Arg Ala Gln Pro Ser Leu Ile Leu Tyr
 1 5 10 15

Val Val Ser Asp Leu Arg Trp Met Glu Phe Arg Thr Ser Cys
 20 25 30

<210> 769

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (46)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 769

Leu Ala Val Ser Thr Ser Phe Ile Cys Cys Ala Asp Ile Ser Thr Ala
 1 5 10 15

Leu Pro Leu Gly Ser Ser Arg Pro Ala Pro Ala Pro Arg His Arg Glu
 20 25 30

His Glu His Gly His Gln Ala Arg Pro Pro Arg Leu Leu Xaa Thr Ser
 35 40 45

Leu Met Pro Leu Ser Thr Pro Ala Ala Ala Gln Leu Trp Thr Gln
 50 55 60

Leu Thr Pro Met Gly Gly Arg Pro Gly Gly Arg His Ser Pro Pro Thr
 65 70 75 80

Leu His Thr Gly Pro Arg Ala Leu Pro Pro Gly Pro Pro His Pro Ser
 85 90 95

Leu His Val Ala Leu Ser Leu Leu Arg
 100 105

<210> 770

<211> 85

423

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 770

Ala	Pro	Ala	Val	Pro	His	Gln	Pro	Pro	Gly	Thr	Glu	Ser	Thr	Ser	Met
1				5					10					15	

Gly	Thr	Lys	Pro	Gly	Leu	Pro	Gly	Cys	Ser	Xaa	Arg	Pro	Leu	Cys	His
		20					25						30		

Tyr	Gln	His	Gln	Leu	Xaa	Pro	Ser	Tyr	Phe	Gly	His	Ser	Ser	Pro	Pro
	35					40						45			

Trp	Gly	Ala	Val	Leu	Val	Gly	Val	Thr	Pro	His	Pro	Arg	Cys	Thr	Pro
	50					55					60				

Ala	Pro	Gly	Pro	Cys	Arg	Leu	Gly	Leu	His	Thr	His	Pro	Cys	Thr	Trp
65					70					75					80

Gln	Leu	Cys	Leu	Cys
				85

<210> 771

<211> 28

<212> PRT

<213> Homo sapiens

<400> 771

Cys	Ala	Asp	Ile	Ser	Thr	Ala	Leu	Pro	Leu	Gly	Ser	Ser	Arg	Pro	Ala
1				5					10					15	

Pro	Ala	Pro	Arg	His	Arg	Glu	His	Glu	His	Gly	His
		20						25			

<210> 772

<211> 25

<212> PRT

<213> Homo sapiens

<400> 772

Trp	Thr	Gln	Leu	Thr	Pro	Met	Gly	Gly	Arg	Pro	Gly	Gly	Arg	His	Ser
1				5					10					15	

Pro	Pro	Thr	Leu	His	Thr	Gly	Pro	Arg
		20					25	

424

<210> 773
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 773
 His Gln Pro Pro Gly Thr Glu Ser Thr Ser Met Gly Thr Lys Pro Gly
 1 5 10 15
 Leu Pro Gly Cys
 20

<210> 774
 <211> 64
 <212> PRT
 <213> Homo sapiens

<400> 774
 Ser Arg Gly Ser Leu Leu Pro Pro His Leu Pro His Arg Val Val Val
 1 5 10 15
 Arg Val His Arg Gly Ala Lys Ser Leu Lys Ala Leu Arg Gln Tyr Ile
 20 25 30
 Gly Ala Ala His Leu Gln Leu Pro Trp Asp Gly Lys Asp Pro Ala Arg
 35 40 45
 Pro Leu Gly Ile Thr Leu Cys Leu Gln Met Glu Ile Gln Val Leu Gly
 50 55 60

<210> 775
 <211> 150
 <212> PRT
 <213> Homo sapiens

<400> 775
 Cys Cys Ser Phe Gly Phe Tyr Tyr Met Val Gly Ser Asp Thr Ala Glu
 1 5 10 15
 Lys Gln Gly Pro Ile Pro Gly Ser Gln Thr Gln Glu Gly Pro Trp Leu
 20 25 30
 Ser Arg His Thr His Ser Pro Arg Ala Val Pro Glu Ser Ser Thr Ala
 35 40 45
 Pro Ala Gln Pro Leu Leu Leu Pro Leu Pro Ala Pro Gln Ala Arg Arg
 50 55 60
 Trp Ala Ser Asn Ala Asn Gly Trp Gly Trp Asp His Gln Arg Glu Gly
 65 70 75 80
 Gln Ala Asn Tyr Pro Tyr Ser Ala Arg Pro Ala Pro His Asn Leu His

425

85

90

95

Pro Gln Tyr Leu Asn Leu His Leu Gln Thr Gln Cys Tyr Ala Gln Gly
 100 105 110

Ser Gly Trp Val Leu Pro Ile Pro Gly Gln Leu Lys Val Gly Gly Pro
 115 120 125

Tyr Ile Leu Pro Glu Gly Leu Gln Gly Leu Cys Ser Ser Val His Pro
 130 135 140

His Asn Asn Pro Val Arg
 145 150

<210> 776

<211> 25

<212> PRT

<213> Homo sapiens

<400> 776

His Arg Gly Ala Lys Ser Leu Lys Ala Leu Arg Gln Tyr Ile Gly Ala
 1 5 10 15

Ala His Leu Gln Leu Pro Trp Asp Gly
 20 25

<210> 777

<211> 21

<212> PRT

<213> Homo sapiens

<400> 777

Pro Ala Pro Gln Ala Arg Arg Trp Ala Ser Asn Ala Asn Gly Trp Gly
 1 5 10 15

Trp Asp His Gln Arg
 20

<210> 778

<211> 23

<212> PRT

<213> Homo sapiens

<400> 778

His Pro Gln Tyr Leu Asn Leu His Leu Gln Thr Gln Cys Tyr Ala Gln
 1 5 10 15

Gly Ser Gly Trp Val Leu Pro
 20

<210> 779

<211> 64

<212> PRT

<213> Homo sapiens

426

<400> 779

Thr Asn Gly Ile Met Gln Tyr Val Thr Phe Cys Val Trp Leu Ile Leu
 1 5 10 15

Phe Ser Ile Met Phe Leu Arg Phe Ile Gln Ala Val Ala Cys Ile Ser
 20 25 30

Thr Ser Phe Leu Phe Leu Ala Glu Tyr Tyr Ser Ile Ile Trp Ile Tyr
 35 40 45

His Asn Ser Phe Thr Tyr Ser Ser Phe Val Ser Ala Val Trp Leu Leu
 50 55 60

<210> 780

<211> 123

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (45)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (46)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 780

Tyr Asn Phe Met Phe Asn Phe Ser Lys Asn Cys Gln Lys Val Phe His
 1 5 10 15

Ser Gly Cys Ile Ile Tyr Ile Pro Thr Gly Asn Val Gln Gly Phe Leu
 20 25 30

Phe Phe His Ile Leu Ala Leu Thr Asn Thr Ser Phe Xaa Xaa Xaa Phe
 35 40 45

Cys Phe Phe Ile Ile Ala Thr Leu Val Asp Val Lys Trp His Leu Ile
 50 55 60

Val Leu Ile Cys Ile Ser Leu Met Thr Asn Asp Ile Ile Leu Phe Leu
 65 70 75 80

Cys Ala Tyr Gly Ser Lys Val Phe Pro Trp Arg Asn Val Pro Ser Ser
 85 90 95

Pro Leu Pro Phe Gln Asn Leu Val Ile Cys Leu Leu Leu Phe Ser Phe

427

100 105 110
 Lys Lys Phe Trp Pro Gly Ala Val Ala His Leu
 115 120

<210> 781
 <211> 91
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (66)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (79)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 781
 Cys Val Thr Gln Ala Arg Val Gln Trp Arg Asp Leu Gly Ser Leu Gln
 1 5 10 15
 Pro Pro Pro Pro Gly Phe Lys Arg Phe Ser Cys Leu Ser Leu Leu Ser
 20 25 30
 Arg Xaa Asp Tyr Met His Leu Pro Pro Arg Pro Ala Asn Phe Cys Ile
 35 40 45
 Phe Ser Lys Met Gly Phe His His Val Gly Gln Ala Gly Leu Glu Val
 50 55 60
 Leu Xaa Ser Ser Asp Leu Pro Ala Leu Ala Ser Gln Ser Ala Xaa Ile
 65 70 75 80
 Thr Gly Glu Pro Leu Arg Leu Ala Arg Ile Ser
 85 90

<210> 782
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 782
 Leu Pro Pro Arg Pro Ala Asn Phe Cys Ile Phe Ser Lys Met Gly Phe
 1 5 10 15
 His His Val Gly Gln Ala Gly Leu Glu
 20 25

428

<210> 783
 <211> 24
 <212> PRT
 <213> Homo sapiens

<400> 783
 Leu Ile Leu Phe Ser Ile Met Phe Leu Arg Phe Ile Gln Ala Val Ala
 1 5 10 15
 Cys Ile Ser Thr Ser Phe Leu Phe
 20

<210> 784
 <211> 90
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (90)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 784
 Ala Leu Val Pro Ser Pro Gln Gln Ile Leu Pro Ser Cys Phe Ser Leu
 1 5 10 15
 Met Trp Gln Val Thr Thr Lys Ser Ala Leu Val Phe Phe Lys Cys Ile
 20 25 30
 Tyr Ile Pro Phe Leu Ser Ala Pro Ser Leu Pro Arg Leu Glu Asn Cys
 35 40 45
 Leu Ile Phe Cys Ser Leu Asp Val Gln Ser Gln Leu Val Phe Leu Ser
 50 55 60
 Ser Pro Pro Val Ala Gly Val Leu Phe Phe Phe Leu Leu Ser Pro Leu
 65 70 75 80
 Gly Ser Lys Ser Cys Ser Thr Val Glu Xaa
 85 90

<210> 785
 <211> 26
 <212> PRT
 <213> Homo sapiens

<400> 785
 Ala Pro Ser Leu Pro Arg Leu Glu Asn Cys Leu Ile Phe Cys Ser Leu
 1 5 10 15
 Asp Val Gln Ser Gln Leu Val Phe Leu Ser
 20 25

<210> 786

429

<211> 13
 <212> PRT
 <213> Homo sapiens

<400> 786
 Ser Ser Pro Ser Arg Val Arg Leu Arg His Thr Pro Gly
 1 5 10

<210> 787
 <211> 76
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (43)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (60)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 787
 Ser Asn Thr Asn Tyr Cys Phe Met Phe Phe Tyr Phe Pro Val Lys Val
 1 5 10 15

Leu Val Pro Phe Lys Asn Cys Tyr Ile Leu Ser Leu Leu Ile Leu Pro
 20 25 30

Cys Cys Ile Cys Gly His Gln Phe Pro Arg Xaa Gln Ala Cys Thr Phe
 35 40 45

Cys Leu His Thr Leu Gly Gly Phe Ser Phe Ser Xaa Leu Phe Leu Val
 50 55 60

Leu Leu Ser Phe Tyr Val Gln Thr Gly Phe Ser Val
 65 70 75

<210> 788
 <211> 119
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (41)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (97)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE

430

<222> (103)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 788

Gly	Thr	Ser	Arg	His	Gly	Gln	Arg	Pro	Ile	Ala	Pro	Gly	Thr	Pro	Trp
1				5					10					15	

Gln	Arg	Glu	Pro	Arg	Val	Glu	Val	Met	Asp	Pro	Ala	Gly	Gly	Pro	Arg
		20						25					30		

Gly	Val	Leu	Pro	Arg	Pro	Cys	Arg	Xaa	Leu	Val	Leu	Leu	Asn	Pro	Arg
		35					40					45			

Gly	Gly	Lys	Gly	Lys	Ala	Leu	Gln	Leu	Phe	Arg	Ser	His	Val	Gln	Pro
	50					55					60				

Leu	Leu	Ala	Glu	Ala	Glu	Ile	Ser	Phe	Thr	Leu	Met	Leu	Thr	Glu	Arg
65					70					75				80	

Arg	Asn	His	Ala	Arg	Glu	Leu	Val	Arg	Ser	Glu	Glu	Leu	Gly	Arg	Trp
			85						90					95	

Xaa	Ala	Leu	Val	Val	Met	Xaa	Gly	Asp	Gly	Leu	Met	His	Glu	Val	Val
		100						105					110		

Asn	Gly	Leu	His	Gly	Ala	Ala
		115				

<210> 789

<211> 24

<212> PRT

<213> Homo sapiens

<400> 789

Arg	Pro	Ile	Ala	Pro	Gly	Thr	Pro	Trp	Gln	Arg	Glu	Pro	Arg	Val	Glu
1				5					10					15	

Val	Met	Asp	Pro	Ala	Gly	Gly	Pro
			20				

<210> 790

<211> 15

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 790

Ala	Ser	Gly	Pro	Leu	Met	Gly	Xaa	Ala	Val	Leu	Lys	Ile	Phe	Glu
1				5					10					15

<210> 791

431

<211> 18
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 791
 Leu Leu Arg Ser Ala Leu Xaa Ser Pro His Leu Pro Thr Pro Val Pro
 1 5 10 15

Leu Val

<210> 792
 <211> 69
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (2)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (24)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (45)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (46)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 792
 Gln Xaa Arg Asn Leu Ala Gln Glu Ala Phe Lys Trp Ile Pro Gln Asp
 1 5 10 15

Arg Pro Thr Val Arg Ser Arg Xaa Arg Met Gly Leu Ser Ile Arg Leu
 20 25 30

Pro Ile Leu Ala Ser Asn Cys Cys Ala Leu Pro Phe Xaa Xaa Pro Thr
 35 40 45

Ser Pro Leu Gln Cys Leu Trp Ser Cys His Cys Ser Phe Gln Ala Asn
 50 55 60

Thr Gly Leu Ala Ser
 65

432

<210> 793
 <211> 59
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (53)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 793
 Gln Met Thr Gln Glu Pro Pro Thr Ser Val Arg Ala His Gly Ile Ala
 1 5 10 15
 Ala Trp Gly Asn Gly Cys Arg Asp Lys Asn Thr Lys Arg Leu Ile Gln
 20 25 30
 Tyr Trp Pro Glu Ser Cys Ser Gly Met Thr Lys Gly Thr Gly Val Gly
 35 40 45
 Arg Trp Gly Glu Xaa Arg Ala Glu Arg Ser Ser
 50 55

<210> 794
 <211> 21
 <212> PRT
 <213> Homo sapiens

<400> 794
 His Gly Ile Ala Ala Trp Gly Asn Gly Cys Arg Asp Lys Asn Thr Lys
 1 5 10 15
 Arg Leu Ile Gln Tyr
 20

<210> 795
 <211> 13
 <212> PRT
 <213> Homo sapiens

<400> 795
 Cys Glu Arg Ser Gly Tyr Thr Arg Met Ala Met Asp Thr
 1 5 10

<210> 796
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 796
 Thr Gly Ser Ile Leu Ala Val Gly Lys Lys Tyr Ser Leu Gly Ser Tyr
 1 5 10 15
 Ser Arg Gly Asp Trp His Met Arg Val Val Gly Leu Arg Gly Leu Gly

20

30

Leu Pro Pro Cys
130

<213> Homo sapiens

Gly Ser Tyr Ser Arg Gly Asp Trp His Met Arg Val Val Gly Leu Arg
1 5 10 15

Gly Leu Gly Ala Ser Thr Leu Gln Gly Leu Leu Ile Gly
20 25

<213> Homo sapiens

Ser Thr Pro Ala Ala Leu Leu Gly Cys Trp Pro Pro Phe Arg Glu Gly
1 5 10 15

Glu Ile Leu Gly Leu Gln Arg Pro Gly Gln Trp
20 25

<213> Homo sapiens

Thr Met Gly Thr Trp Val Asp Trp Leu Thr Thr Asn Thr Ala His Thr
1. 5 10 15

434

Pro Ala Ile Ala Ala Ala Ile Cys Ala Glu Asp Phe Pro Gln Arg His
 20 25 30

Cys Gly Ser Val Glu Arg Ser Pro Asp Gln Ala Cys
 35 40

<210> 800
 <211> 23
 <212> PRT
 <213> Homo sapiens

<400> 800
 Thr Asn Thr Ala His Thr Pro Ala Ile Ala Ala Ala Ile Cys Ala Glu
 1 5 10 15

Asp Phe Pro Gln Arg His Cys
 20

<210> 801
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 801
 Met Ser Pro Glu Thr Lys Gly Lys Gly Arg Ser Phe Pro Leu Lys
 1 5 10 15

<210> 802
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 802
 Cys Gln Asn Lys Cys Ser Glu Thr Thr Cys Gly Arg Thr Arg Arg Glu
 1 5 10 15

Ser Asn Lys Gln Ala Arg Ala Met Ala Phe Ile Phe Lys Gly Lys Asp
 20 25 30

Leu Pro Phe Pro Phe Val Ser Gly Asp Ile Gln Pro Lys Ser Ser Gly
 35 40 45

Ser Met Ala Pro Asp Gln Gln Gly Leu Cys Tyr Leu Gly Ser Trp Arg
 50 55 60

Ser His Leu Tyr Cys Arg Leu Leu Pro Met Asp Gln Val Ser Pro Ala
 65 70 75 80

Leu Cys

<210> 803
 <211> 63

435

<212> PRT

<213> Homo sapiens

<400> 803

Lys Pro Ser Pro Gly Leu Ala Tyr Cys Ser Leu Ser Trp Ser Phe His
1 5 10 15

Met Leu Phe Leu Asn Ile Cys Ser Gly Ile Thr Ile Pro Val Ile Leu
20 25 30

Ser Ser Gly Pro Ser His Leu Ser Thr Leu Ser Leu Ala Val Ser Pro
35 40 45

Arg Arg Pro Gly Thr Trp Val Lys Ala Cys Ser Cys Trp Cys Pro
50 55 60

<210> 804

<211> 25

<212> PRT

<213> Homo sapiens

<400> 804

Asn Lys Gln Ala Arg Ala Met Ala Phe Ile Phe Lys Gly Lys Asp Leu
1 5 10 15

Pro Phe Pro Phe Val Ser Gly Asp Ile
20 25

<210> 805

<211> 21

<212> PRT

<213> Homo sapiens

<400> 805

Tyr Leu Gly Ser Trp Arg Ser His Leu Tyr Cys Arg Leu Leu Pro Met
1 5 10 15

Asp Gln Val Ser Pro
20

<210> 806

<211> 25

<212> PRT

<213> Homo sapiens

<400> 806

Gly Ile Thr Ile Pro Val Ile Leu Ser Ser Gly Pro Ser His Leu Ser
1 5 10 15

Thr Leu Ser Leu Ala Val Ser Pro Arg
20 25

<210> 807

<211> 11

436

<212> PRT

<213> Homo sapiens

<400> 807

Leu Glu Arg Leu Gly Val Gly Arg Gly Leu Glu
 1 5 10

<210> 808

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (55)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 808

Asp Leu Pro Pro Cys Trp Thr Thr Leu Lys Glu His Gln Cys Phe Met
 1 5 10 15

Gln Tyr Gln Leu Phe Thr Ile Gln Cys Lys Val Val Glu Gln Thr Ile
 20 25 30

Cys Glu Asp Glu Arg Lys Met Glu Ser Thr Cys Leu Thr Leu Ala Xaa
 35 40 45

Pro Glu Ser Val Arg Gln Xaa Cys Pro Ala Thr Leu Trp Ser Ser Met
 50 55 60

Asn Ile Cys
 65

<210> 809

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 809

Thr Asn Arg Val Xaa Leu Ser Trp Arg Lys Glu Glu Gln Arg Met Gly
 1 5 10 15

Arg Thr Glu Thr Gly Ala Lys Asp Lys Gly Arg Asp Phe Leu Glu Arg
 20 25 30

Gly Ser Arg Gly Trp Gln Leu Tyr Thr Gly Ala Ala Asp Thr Glu Glu

437

35

40

45

Val

<210> 810

<211> 207

<212> PRT

<213> Homo sapiens

<400> 810

Glu Gln Val Leu Ala Leu Leu Trp Pro Arg Phe Glu Leu Ile Leu Glu
 1 5 10 15

Met Asn Val Gln Ser Val Arg Ser Thr Asp Pro Gln Arg Leu Gly Gly
 20 25 30

Leu Asp Thr Arg Pro His Tyr Ile Thr Arg Arg Tyr Ala Glu Phe Ser
 35 40 45

Ser Ala Leu Val Ser Ile Asn Gln Thr Ile Pro Asn Glu Arg Thr Met
 50 55 60

Gln Leu Leu Gly Gln Leu Gln Val Glu Val Glu Asn Phe Val Leu Arg
 65 70 75 80

Val Ala Ala Glu Phe Ser Ser Arg Lys Glu Gln Leu Val Phe Leu Ile
 85 90 95

Asn Asn Tyr Asp Met Met Leu Gly Val Leu Met Glu Arg Ala Ala Asp
 100 105 110

Asp Ser Lys Glu Val Glu Ser Phe Gln Gln Leu Leu Asn Ala Arg Thr
 115 120 125

Gln Glu Phe Ile Glu Glu Leu Leu Ser Pro Pro Phe Gly Gly Leu Val
 130 135 140

Ala Phe Val Lys Glu Ala Glu Ala Leu Ile Glu Arg Gly Gln Ala Glu
 145 150 155 160

Arg Leu Arg Gly Glu Glu Ala Arg Val Thr Gln Leu Ile Arg Gly Phe
 165 170 175

Gly Ser Ser Trp Lys Ser Ser Val Glu Ser Leu Ser Gln Asp Val Met
 180 185 190

Arg Ser Phe Thr Asn Phe Arg Asn Gly Thr Ser Ile Ile Gln Gly
 195 200 205

<210> 811

<211> 110

<212> PRT

<213> Homo sapiens

<220>

438

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 811

Ala	Leu	Leu	Lys	Tyr	Arg	Phe	Phe	Tyr	Gln	Phe	Leu	Leu	Gly	Asn	Glu
1			5						10					15	

Arg	Ala	Thr	Ala	Lys	Glu	Ile	Arg	Asp	Glu	Tyr	Val	Glu	Thr	Leu	Ser
	20						25						30		

Lys	Ile	Tyr	Leu	Ser	Tyr	Tyr	Arg	Ser	Tyr	Leu	Gly	Arg	Leu	Met	Lys
	35						40					45			

Val	Gln	Tyr	Glu	Glu	Val	Ala	Glu	Lys	Asp	Asp	Leu	Met	Gly	Val	Glu
	50					55					60				

Asp	Thr	Ala	Lys	Lys	Gly	Phe	Xaa	Ser	Lys	Pro	Ser	Leu	Arg	Ser	Arg
65					70					75					80

Asn	Thr	Ile	Phe	Thr	Leu	Gly	Thr	Arg	Gly	Ser	Val	Ile	Ser	Pro	Thr
			85						90						95

Glu	Leu	Glu	Ala	Pro	Ile	Leu	Val	Pro	His	Thr	Ala	Gln	Arg
			100					105					110

<210> 812

<211> 97

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (16)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 812

Glu	Gln	Arg	Tyr	Pro	Phe	Glu	Ala	Leu	Phe	Arg	Ser	Gln	His	Tyr	Xaa
1				5					10					15	

Leu	Leu	Asp	Asn	Ser	Cys	Arg	Glu	Tyr	Leu	Phe	Ile	Cys	Glu	Phe	Phe
		20						25					30		

Val	Val	Ser	Gly	Pro	Xaa	Ala	His	Asp	Leu	Phe	His	Ala	Val	Met	Gly
		35					40					45			

Arg	Thr	Leu	Ser	Met	Thr	Leu	Lys	His	Leu	Asp	Ser	Tyr	Leu	Ala	Asp
	50					55					60				

Cys	Tyr	Asp	Ala	Ile	Ala	Val	Phe	Leu	Cys	Ile	His	Ile	Val	Leu	Arg
65					70					75					80

439

Phe Arg Asn Ile Ala Ala Lys Arg Asp Val Pro Ala Leu Asp Arg Tyr
85 90 95

Trp

<210> 813

<211> 26

<212> PRT

<213> Homo sapiens

<400> 813

Gly Gly Leu Asp Thr Arg Pro His Tyr Ile Thr Arg Arg Tyr Ala Glu
1 5 10 15

Phe Ser Ser Ala Leu Val Ser Ile Asn Gln
20 25

<210> 814

<211> 20

<212> PRT

<213> Homo sapiens

<400> 814

Ser Arg Lys Glu Gln Leu Val Phe Leu Ile Asn Asn Tyr Asp Met Met
1 5 10 15

Leu Gly Val Leu
20

<210> 815

<211> 411

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (127)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (149)

<223> Xaa equals any of the naturally occurring L-amino acids

440

<400> 815

Ala Leu Leu Lys Tyr Arg Phe Phe Tyr Gln Phe Leu Leu Gly Asn Glu
 1 5 10 15
 Arg Ala Thr Ala Lys Glu Ile Arg Asp Glu Tyr Val Glu Thr Leu Ser
 20 25 30
 Lys Ile Tyr Leu Ser Tyr Tyr Arg Ser Tyr Leu Gly Arg Leu Met Lys
 35 40 45
 Val Gln Tyr Glu Glu Val Ala Glu Lys Asp Asp Leu Met Gly Val Glu
 50 55 60
 Asp Thr Ala Lys Lys Gly Phe Xaa Ser Lys Pro Ser Leu Arg Ser Arg
 65 70 75 80
 Asn Thr Ile Phe Thr Leu Gly Thr Arg Gly Ser Val Ile Ser Pro Thr
 85 90 95
 Glu Leu Glu Ala Pro Ile Leu Val Pro His Thr Ala Gln Arg Xaa Glu
 100 105 110
 Gln Arg Tyr Pro Phe Glu Ala Leu Phe Arg Ser Gln His Tyr Xaa Leu
 115 120 125
 Leu Asp Asn Ser Cys Arg Glu Tyr Leu Phe Ile Cys Glu Phe Phe Val
 130 135 140
 Val Ser Gly Pro Xaa Ala His Asp Leu Phe His Ala Val Met Gly Arg
 145 150 155 160
 Thr Leu Ser Met Thr Leu Lys His Leu Asp Ser Tyr Leu Ala Asp Cys
 165 170 175
 Tyr Asp Ala Ile Ala Val Phe Leu Cys Ile His Ile Val Leu Arg Phe
 180 185 190
 Arg Asn Ile Ala Ala Lys Arg Asp Val Pro Ala Leu Asp Arg Tyr Trp
 195 200 205
 Glu Gln Val Leu Ala Leu Leu Trp Pro Arg Phe Glu Leu Ile Leu Glu
 210 215 220
 Met Asn Val Gln Ser Val Arg Ser Thr Asp Pro Gln Arg Leu Gly Gly
 225 230 235 240
 Leu Asp Thr Arg Pro His Tyr Ile Thr Arg Arg Tyr Ala Glu Phe Ser
 245 250 255
 Ser Ala Leu Val Ser Ile Asn Gln Thr Ile Pro Asn Glu Arg Thr Met
 260 265 270
 Gln Leu Leu Gly Gln Leu Gln Val Glu Val Glu Asn Phe Val Leu Arg
 275 280 285
 Val Ala Ala Glu Phe Ser Ser Arg Lys Glu Gln Leu Val Phe Leu Ile
 290 295 300

441

Asn Asn Tyr Asp Met Met Leu Gly Val Leu Met Glu Arg Ala Ala Asp
 305 310 315 320
 Asp Ser Lys Glu Val Glu Ser Phe Gln Gln Leu Leu Asn Ala Arg Thr
 325 330 335
 Gln Glu Phe Ile Glu Glu Leu Leu Ser Pro Pro Phe Gly Gly Leu Val
 340 345 350
 Ala Phe Val Lys Glu Ala Glu Ala Leu Ile Glu Arg Gly Gln Ala Glu
 355 360 365
 Arg Leu Arg Gly Glu Glu Ala Arg Val Thr Gln Leu Ile Arg Gly Phe
 370 375 380
 Gly Ser Ser Trp Lys Ser Ser Val Glu Ser Leu Ser Gln Asp Val Met
 385 390 395 400
 Arg Ser Phe Thr Asn Phe Arg Asn Gly Thr Ser
 405 410

<210> 816
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 816
 Pro Ala Asp Leu Arg Ala Val Ser Gly Thr Ser Glu Val Gly Leu Met
 1 5 10 15
 Leu Leu Glu Leu His His Lys Val Val Asn Val Asp Glu Leu Ser Pro
 20 25 30
 Gly Arg Glu Gly Ser Glu Leu Arg Leu Gly Gln His Pro Val Glu Ala
 35 40 45
 Met Ile Glu Leu Asp Gln Leu Gly Gln Arg Ser Leu Asn Asp Thr Gly
 50 55 60
 Ala Ile Ser Glu Val Gly Glu Thr Pro His Tyr Ile Leu Thr Gln Arg
 65 70 75 80
 Phe His

<210> 817
 <211> 120
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (12)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <220>

442

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 817

Gly Pro His Pro Gly Ala Ser His Ser Ala Ala Xaa Glu Gln Arg Tyr
 1 5 10 15
 Pro Phe Glu Ala Leu Phe Arg Ser Gln His Tyr Xaa Leu Leu Asp Asn
 20 25 30
 Ser Cys Arg Glu Tyr Leu Phe Ile Cys Glu Phe Phe Val Val Ser Gly
 35 40 45
 Pro Xaa Ala His Asp Leu Phe His Ala Val Met Gly Arg Thr Leu Ser
 50 55 60
 Met Thr Leu Lys His Leu Asp Ser Tyr Leu Ala Asp Cys Tyr Asp Ala
 65 70 75 80
 Ile Ala Val Phe Leu Cys Ile His Ile Val Leu Arg Phe Arg Asn Ile
 85 90 95
 Ala Ala Lys Arg Asp Val Pro Ala Leu Asp Arg Tyr Trp Gly Thr Gly
 100 105 110
 Ala Cys Leu Ala Met Ala Thr Val
 115 120

<210> 818

<211> 303

<212> PRT

<213> Homo sapiens

<400> 818

Tyr Glu Gly Lys Glu Phe Asp Tyr Val Phe Ser Ile Asp Val Asn Glu
 1 5 10 15
 Gly Gly Pro Ser Tyr Lys Leu Pro Tyr Asn Thr Ser Asp Asp Pro Trp
 20 25 30
 Leu Thr Ala Tyr Asn Phe Leu Gln Lys Asn Asp Leu Asn Pro Met Phe
 35 40 45
 Leu Asp Gln Val Ala Lys Phe Ile Ile Asp Asn Thr Lys Gly Gln Met
 50 55 60
 Leu Gly Leu Gly Asn Pro Ser Phe Ser Asp Pro Phe Thr Gly Gly Gly
 65 70 75 80
 Arg Tyr Val Pro Gly Ser Ser Gly Ser Ser Asn Thr Leu Pro Thr Ala
 85 90 95

443

Asp Pro Phe Thr Gly Ala Gly Arg Tyr Val Pro Gly Ser Ala Ser Met
 100 105 110
 Gly Thr Thr Met Ala Gly Val Asp Pro Phe Thr Gly Asn Ser Ala Tyr
 115 120 125
 Arg Ser Ala Ala Ser Lys Thr Met Asn Ile Tyr Phe Pro Lys Lys Glu
 130 135 140
 Ala Val Thr Phe Asp Gln Ala Asn Pro Thr Gln Ile Leu Gly Lys Leu
 145 150 155 160
 Lys Glu Leu Asn Gly Thr Ala Pro Glu Glu Lys Lys Leu Thr Glu Asp
 165 170 175
 Asp Leu Ile Leu Leu Glu Lys Ile Leu Ser Leu Ile Cys Asn Ser Ser
 180 185 190
 Ser Glu Lys Pro Thr Val Gln Gln Leu Gln Ile Leu Trp Lys Ala Ile
 195 200 205
 Asn Cys Pro Glu Asp Ile Val Phe Pro Ala Leu Asp Ile Leu Arg Leu
 210 215 220
 Ser Ile Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu
 225 230 235 240
 Gly Ala Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro Lys Gly
 245 250 255
 Lys Pro Ala Asn Gln Leu Leu Ala Leu Arg Thr Phe Cys Asn Cys Phe
 260 265 270
 Val Gly Gln Ala Gly Gln Lys Leu Met Met Ser Gln Arg Glu Ser Leu
 275 280 285
 Met Ser His Ala Ile Glu Leu Lys Ser Gly Ser Asn Lys Asn Ile
 290 295 300

<210> 819

<211> 18

<212> PRT

<213> Homo sapiens

<400> 819

His Ile Ala Leu Ala Thr Leu Ala Leu Asn Tyr Ser Val Cys Phe His
 1 5 10 15

Lys Asp

<210> 820

<211> 49

<212> PRT

<213> Homo sapiens

444

<400> 820

His Asn Ile Glu Gly Lys Ala Gln Cys Leu Ser Leu Ile Ser Thr Ile
 1 5 10 15

Leu Glu Val Val Gln Asp Leu Glu Ala Thr Phe Arg Leu Leu Val Ala
 20 25 30

Leu Gly Thr Leu Ile Ser Asp Asp Ser Asn Ala Val Gln Leu Ala Lys
 35 40 45

Ser

<210> 821

<211> 30

<212> PRT

<213> Homo sapiens

<400> 821

Leu Gly Val Asp Ser Gln Ile Lys Lys Tyr Ser Ser Val Ser Glu Pro
 1 5 10 15

Ala Lys Val Ser Glu Cys Cys Arg Phe Ile Leu Asn Leu Leu
 20 25 30

<210> 822

<211> 400

<212> PRT

<213> Homo sapiens

<400> 822

Tyr Glu Gly Lys Glu Phe Asp Tyr Val Phe Ser Ile Asp Val Asn Glu
 1 5 10 15

Gly Gly Pro Ser Tyr Lys Leu Pro Tyr Asn Thr Ser Asp Asp Pro Trp
 20 25 30

Leu Thr Ala Tyr Asn Phe Leu Gln Lys Asn Asp Leu Asn Pro Met Phe
 35 40 45

Leu Asp Gln Val Ala Lys Phe Ile Ile Asp Asn Thr Lys Gly Gln Met
 50 55 60

Leu Gly Leu Gly Asn Pro Ser Phe Ser Asp Pro Phe Thr Gly Gly Gly
 65 70 75 80

Arg Tyr Val Pro Gly Ser Ser Gly Ser Ser Asn Thr Leu Pro Thr Ala
 85 90 95

Asp Pro Phe Thr Gly Ala Gly Arg Tyr Val Pro Gly Ser Ala Ser Met
 100 105 110

Gly Thr Thr Met Ala Gly Val Asp Pro Phe Thr Gly Asn Ser Ala Tyr
 115 120 125

445

Arg Ser Ala Ala Ser Lys Thr Met Asn Ile Tyr Phe Pro Lys Lys Glu
 130 135 140
 Ala Val Thr Phe Asp Gln Ala Asn Pro Thr Gln Ile Leu Gly Lys Leu
 145 150 155 160
 Lys Glu Leu Asn Gly Thr Ala Pro Glu Glu Lys Lys Leu Thr Glu Asp
 165 170 175
 Asp Leu Ile Leu Leu Glu Lys Ile Leu Ser Leu Ile Cys Asn Ser Ser
 180 185 190
 Ser Glu Lys Pro Thr Val Gln Gln Leu Gln Ile Leu Trp Lys Ala Ile
 195 200 205
 Asn Cys Pro Glu Asp Ile Val Phe Pro Ala Leu Asp Ile Leu Arg Leu
 210 215 220
 Ser Ile Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu
 225 230 235 240
 Gly Ala Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro Lys Gly
 245 250 255
 Lys Pro Ala Asn Gln Leu Leu Ala Leu Arg Thr Phe Cys Asn Cys Phe
 260 265 270
 Val Gly Gln Ala Gly Gln Lys Leu Met Met Ser Gln Arg Glu Ser Leu
 275 280 285
 Met Ser His Ala Ile Glu Leu Lys Ser Gly Ser Asn Lys Asn Ile His
 290 295 300
 Ile Ala Leu Ala Thr Leu Ala Leu Asn Tyr Ser Val Cys Phe His Lys
 305 310 315 320
 Asp His Asn Ile Glu Gly Lys Ala Gln Cys Leu Ser Leu Ile Ser Thr
 325 330 335
 Ile Leu Glu Val Val Gln Asp Leu Glu Ala Thr Phe Arg Leu Leu Val
 340 345 350
 Ala Leu Gly Thr Leu Ile Ser Asp Asp Ser Asn Ala Val Gln Leu Ala
 355 360 365
 Lys Ser Leu Gly Val Asp Ser Gln Ile Lys Lys Tyr Ser Ser Val Ser
 370 375 380
 Glu Pro Ala Lys Val Ser Glu Cys Cys Arg Phe Ile Leu Asn Leu Leu
 385 390 395 400

<210> 823

<211> 29

<212> PRT

446

<213> Homo sapiens

<400> 823

Leu Asn Leu Leu Leu Ile Thr Gln Lys Val Lys Cys Trp Asp Leu Gly
1 5 10 15

Ile Pro Ala Phe Gln Ile His Leu Gln Val Val Val Gly
20 25

<210> 824

<211> 29

<212> PRT

<213> Homo sapiens

<400> 824

Ile Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu Gly
1 5 10 15

Ala Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro
20 25

<210> 825

<211> 22

<212> PRT

<213> Homo sapiens

<400> 825

Ala Ile Glu Leu Lys Ser Gly Ser Asn Lys Asn Ile His Ile Ala Leu
1 5 10 15

Ala Thr Leu Ala Leu Asn
20

<210> 826

<211> 23

<212> PRT

<213> Homo sapiens

<400> 826

Val Gln Leu Ala Lys Ser Leu Gly Val Asp Ser Gln Ile Lys Lys Tyr
1 5 10 15

Ser Ser Val Ser Glu Pro Ala
20

<210> 827

<211> 26

<212> PRT

<213> Homo sapiens

<400> 827

Tyr Glu Gly Lys Glu Phe Asp Tyr Val Phe Ser Ile Asp Val Asn Glu
1 5 10 15

447

Gly Gly Pro Ser Tyr Lys Leu Pro Tyr Asn
 20 25

<210> 828
 <211> 26
 <212> PRT
 <213> Homo sapiens

<400> 828
 Ala Tyr Asn Phe Leu Gln Lys Asn Asp Leu Asn Pro Met Phe Leu Asp
 1 5 10 15

Gln Val Ala Lys Phe Ile Ile Asp Asn Thr
 20 25

<210> 829
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 829
 Ser Phe Ser Asp Pro Phe Thr Gly Gly Gly Arg Tyr Val Pro Gly
 1 5 10 15

<210> 830
 <211> 11
 <212> PRT
 <213> Homo sapiens

<400> 830
 Thr Ala Asp Pro Phe Thr Gly Ala Gly Arg Tyr
 1 5 10

<210> 831
 <211> 19
 <212> PRT
 <213> Homo sapiens

<400> 831
 Thr Thr Met Ala Gly Val Asp Pro Phe Thr Gly Asn Ser Ala Tyr Arg
 1 5 10 15

Ser Ala Ala

<210> 832
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 832
 Asn Ile Tyr Phe Pro Lys Lys Glu Ala
 1 5

448

<210> 833
 <211> 19
 <212> PRT
 <213> Homo sapiens

<400> 833
 Thr Phe Asp Gln Ala Asn Pro Thr Gln Ile Leu Gly Lys Leu Lys Glu
 1 5 10 15

Leu Asn Gly

<210> 834
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 834
 Pro Glu Asp Ile Val Phe Pro Ala Leu Asp Ile Leu Arg Leu Ser Ile
 1 5 10 15

Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu
 20 25 30

<210> 835
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 835
 Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro Lys Gly Lys Pro
 1 5 10 15

Ala Asn Gln Leu Leu Ala Leu Arg Thr Phe Cys Asn Cys Phe Val
 20 25 30

<210> 836
 <211> 26
 <212> PRT
 <213> Homo sapiens

<400> 836
 Gln Ala Gly Gln Lys Leu Met Met Ser Gln Arg Glu Ser Leu Met Ser
 1 5 10 15

His Ala Ile Glu Leu Lys Ser Gly Ser Asn
 20 25

<210> 837
 <211> 139
 <212> PRT
 <213> Homo sapiens

449

<400> 837

Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu His Glu
 1 5 10 15
 His Ile Gln Arg Leu Ser Lys Val Val Thr Ala Asn His Arg Ala Leu
 20 25 30
 Gln Ile Pro Glu Val Tyr Leu Arg Glu Ala Pro Trp Pro Ser Ala Gln
 35 40 45
 Ser Glu Ile Arg Thr Ile Ser Ala Tyr Lys Thr Pro Arg Asp Lys Val
 50 55 60
 Gln Cys Ile Leu Arg Met Cys Ser Thr Ile Met Asn Leu Leu Ser Leu
 65 70 75 80
 Ala Asn Glu Asp Ser Val Pro Gly Ala Asp Asp Phe Val Pro Val Leu
 85 90 95
 Val Phe Val Leu Ile Lys Ala Asn Pro Pro Cys Leu Leu Ser Thr Val
 100 105 110
 Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys Leu Ser Gly Glu Glu Ser
 115 120 125
 Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu
 130 135

<210> 838

<211> 144

<212> PRT

<213> Homo sapiens

<400> 838

Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu His Glu
 1 5 10 15
 His Ile Gln Arg Leu Ser Lys Val Val Thr Ala Asn His Arg Ala Leu
 20 25 30
 Gln Ile Pro Glu Val Tyr Leu Arg Glu Ala Pro Trp Pro Ser Ala Gln
 35 40 45
 Ser Glu Ile Arg Thr Ile Ser Ala Tyr Lys Thr Pro Arg Asp Lys Val
 50 55 60
 Gln Cys Ile Leu Arg Met Cys Ser Thr Ile Met Asn Leu Leu Ser Leu
 65 70 75 80
 Ala Asn Glu Asp Ser Val Pro Gly Ala Asp Asp Phe Val Pro Val Leu
 85 90 95
 Val Phe Val Leu Ile Lys Ala Asn Pro Pro Cys Leu Leu Ser Thr Val
 100 105 110
 Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys Leu Ser Gly Glu Glu Ser

450

115

120

125

Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu Phe Ile Lys Thr Ile
 130 135 140

<210> 839
 <211> 14
 <212> PRT
 <213> Homo sapiens

<400> 839
 Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu
 1 5 10

<210> 840
 <211> 11
 <212> PRT
 <213> Homo sapiens

<400> 840
 Glu Ala Pro Trp Pro Ser Ala Gln Ser Glu Ile
 1 5 10

<210> 841
 <211> 21
 <212> PRT
 <213> Homo sapiens

<400> 841
 Ser Gly Glu Glu Ser Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu
 1 5 10 15

Phe Ile Lys Thr Ile
 20

<210> 842
 <211> 18
 <212> PRT
 <213> Homo sapiens

<400> 842
 Ala Asp Asp Phe Val Pro Val Leu Val Phe Val Leu Ile Lys Ala Asn
 1 5 10 15

Pro Pro

<210> 843
 <211> 12
 <212> PRT

451

<213> Homo sapiens

<400> 843

Tyr Lys Thr Pro Arg Asp Lys Val Gln Cys Ile Leu
1 5 10

<210> 844

<211> 15

<212> PRT

<213> Homo sapiens

<400> 844

Gly Ala Asp Asp Phe Val Pro Val Leu Val Phe Val Leu Ile Lys
1 5 10 15

<210> 845

<211> 12

<212> PRT

<213> Homo sapiens

<400> 845

Pro Val Leu Val Phe Val Leu Ile Lys Ala Asn Pro
1 5 10

<210> 846

<211> 17

<212> PRT

<213> Homo sapiens

<400> 846

Ser Ala Arg Ala Ser Thr Gln Pro Pro Ala Gly Gln His Pro Gly Pro
1 5 10 15

Cys

<210> 847

<211> 33

<212> PRT

<213> Homo sapiens

<400> 847

Met Pro Gly Arg Trp Arg Trp Gln Arg Asp Met His Pro Ala Arg Lys
1 5 10 15

Leu Leu Ser Leu Leu Phe Leu Ile Leu Met Gly Thr Glu Leu Thr Gln
20 25 30

Asp

<210> 848

<211> 19

452

<212> PRT

<213> Homo sapiens

<400> 848

Ser Ala Ala Pro Asp Ser Leu Leu Arg Ser Ser Lys Gly Ser Thr Arg
1 5 10 15

Gly Ser Leu

<210> 849

<211> 20

<212> PRT

<213> Homo sapiens

<400> 849

Ala Ala Ile Val Ile Trp Arg Gly Lys Ser Glu Ser Arg Ile Ala Lys
1 5 10 15

Thr Pro Gly Ile
20

<210> 850

<211> 17

<212> PRT

<213> Homo sapiens

<400> 850

Pro Leu Gly Ile Thr Leu Pro Leu Gly Ala Pro Glu Thr Gly Gly Gly
1 5 10 15

Asp

<210> 851

<211> 20

<212> PRT

<213> Homo sapiens

<400> 851

Cys Ala Ala Glu Thr Trp Lys Gly Ser Gln Arg Ala Gly Gln Leu Cys
1 5 10 15

Ala Leu Leu Ala
20

<210> 852

<211> 20

<212> PRT

<213> Homo sapiens

<400> 852

Phe Arg Gly Gly Gly Thr Leu Val Leu Pro Pro Thr His Thr Pro Glu
1 5 10 15

453

Trp Leu Ile Leu
20

<210> 853
<211> 28
<212> PRT
<213> Homo sapiens

<400> 853
Asn Ser Ala Arg Ala Ser Thr Gln Pro Pro Ala Gly Gln His Pro Gly
1 5 10 15

Pro Cys Met Pro Gly Arg Trp Arg Trp Gln Arg Asp
20 25

<210> 854
<211> 80
<212> PRT
<213> Homo sapiens

<400> 854
Tyr Ile Val Gln Gly Thr Thr Ser Pro Phe Glu Met Pro Thr Ile Pro
1 5 10 15

Thr Pro Ala Arg His Arg Ala Pro His Ser Pro Pro Ala Gly His Val
20 25 30

Ala Thr Ala Pro Gln Ala Leu His Ile Lys Pro Ala Met His Thr Ala
35 40 45

Gly Arg His Ala Gly Cys Pro Ser Arg Ser Gln Arg His Asn Pro His
50 55 60

Arg Leu Phe Leu Glu Pro Pro Arg Ala Ala Leu Cys Pro Lys Gly Gly
65 70 75 80

<210> 855
<211> 97
<212> PRT
<213> Homo sapiens

<400> 855
Ala Ser Asn Ala His Ser Trp Pro Ala Arg Trp Leu Pro Phe Gln Val
1 5 10 15

Ser Ala Ala Gln Ser Pro Pro Pro Val Ser Gly Ala Pro Lys Gly Ser
20 25 30

Val Met Pro Lys Gly Arg Met Ser His Ser Gly Val Cys Val Gly Gly
35 40 45

454

Arg Thr Lys Val Pro Pro Pro Leu Lys Met Pro Gly Val Leu Ala Ile
 50 55 60

Arg Leu Ser Leu Phe Pro Leu Gln Met Thr Ile Ala Ala Lys Asp Pro
 65 70 75 80

Leu Val Leu Pro Phe Glu Leu Leu Ser Arg Glu Ser Gly Ala Ala Glu
 85 90 95

Ser

<210> 856

<211> 27

<212> PRT

<213> Homo sapiens

<400> 856

Gly Arg Met Ser His Ser Gly Val Cys Val Gly Gly Arg Thr Lys Val
 1 5 10 15

Pro Pro Pro Leu Lys Met Pro Gly Val Leu Ala
 20 25

<210> 857

<211> 13

<212> PRT

<213> Homo sapiens

<400> 857

Gly His Gln Thr Ala Pro Glu Thr Pro Ser Arg Ser Asp
 1 5 10

<210> 858

<211> 5

<212> PRT

<213> Homo sapiens

<400> 858

Ser Gln Thr Asp Arg
 1 5

<210> 859

<211> 22

<212> PRT

<213> Homo sapiens

<400> 859

Asn Ile Tyr Phe Lys Glu Lys Arg Lys Arg Gly Gly Ala Lys Met Ala
 1 5 10 15

Gly Ala Ile Ile Glu Asn
 20

455

<210> 860
 <211> 147
 <212> PRT
 <213> Homo sapiens

<400> 860
 Val Tyr Leu Cys Ala Tyr Thr Ser Thr Ile Asn Val Thr Val Thr Thr
 1 5 10 15
 Ala Asn Ala Lys Leu Ile Asn Met Cys Cys Leu Val Asp Ser Asn Thr
 20 25 30
 Arg Ser Cys Val Val Ile Asp Glu Gly Ile Phe Arg Ser Ala Glu Gln
 35 40 45
 Phe Leu Ile Lys Phe Arg Asn Lys Gln Ser Thr Ile Phe Pro Arg Phe
 50 55 60
 Thr Trp Glu Leu His Ser Ile Gly Leu Val Phe Ser Ile Val Phe Met
 65 70 75 80
 Gly Trp Cys Ile Gln Glu His Gln Ser Lys Asp Ile Gln Ile Pro His
 85 90 95
 Pro Ile Asp Ala Cys Glu Lys Gly Thr Val His Leu Asp Cys Asp Ala
 100 105 110
 Ala Pro Phe Pro Met Ala Phe Arg Tyr Leu Thr Asn Asp Glu Glu Asp
 115 120 125
 Asp Ser His Gly Ser Ala Gly Gln Gly Asp Lys His Glu Glu Leu Glu
 130 135 140
 Pro Lys Asn
 145

<210> 861
 <211> 112
 <212> PRT
 <213> Homo sapiens

<400> 861
 Lys Met Pro Cys Arg Met Ser Pro Asn Ser Ser Ile Gln Val Gln Ser
 1 5 10 15
 Asn Pro Met Glu Asn His Ser Thr Gly Ile Leu Ile Lys Val Met Glu
 20 25 30
 Ile Pro Arg Ala Lys Met Thr Phe Ser Arg Ser Thr Gly Gly Arg Asp
 35 40 45
 Ile Met Val Ile Leu Leu Gln Tyr His Thr Ile Met Met Lys Met Leu
 50 55 60
 Gly Val Arg Lys Val Phe Met Ala Asn His Thr Leu Val Lys Pro Pro
 65 70 75 80

456

Thr Leu Ile Phe Phe Phe Ser Phe Thr Gly Ser Arg Met Phe Lys Arg
100 105 110

Leu Gly Leu Trp Pro Ile Ser Phe Thr Phe
65 70

Glu Leu His Ser Ile Gly Leu Val Phe Ser Ile Val Phe Met Gly
20 25 30

Ile Leu Ile Lys Val Met Glu Ile Pro Arg Ala Lys Met
20 25

457

<210> 865

<211> 33

<212> PRT

<213> Homo sapiens

<400> 865

Leu Gly Val Arg Lys Val Phe Met Ala Asn His Thr Leu Val Lys Pro
 1 5 10 15

Pro Phe Trp Trp Ile Pro Thr Asn Arg Ile Ser Phe Ile Ser Pro Ile
 20 25 30

Pro

<210> 866

<211> 9

<212> PRT

<213> Homo sapiens

<400> 866

Thr Met Ala Ser Met Gly Leu Gln Val
 1 5

<210> 867

<211> 167

<212> PRT

<213> Homo sapiens

<400> 867

Lys Ser Trp Met Met Leu Trp Ala Val Gln Asp Thr Gly Thr Ile Thr
 1 5 10 15

Ile Arg Pro Ala Asn Arg Asn Thr Thr Pro Ala Thr Ile Met Val Leu
 20 25 30

Ala Leu Ala Leu Ser Ser Ser Arg Gln Leu Val His Leu Pro Pro Thr
 35 40 45

Thr Asp Ser Ser Thr Pro Arg Ala Ala Thr Met Met Leu Met Met Thr
 50 55 60

Arg Ala Arg Ala Ala Cys Arg Ser Cys Gly Ser Ala Ser Ser Glu Ser
 65 70 75 80

Tyr Thr Leu His Cys Ile Trp Pro Val Leu Cys Thr Thr Gln Phe Ile
 85 90 95

His Arg Pro Ser Gln Met Val Cys Glu Val Thr Met Leu Leu Pro Met
 100 105 110

Lys Ala Val Thr Arg His Met Gly Ser Ala Gln His Ser Met Thr Ala
 115 120 125

Ser Gln Pro Arg Thr Ala Ser Ala Met Pro Ile Thr Cys Ser Pro Met

458

130 135 140
 Glu Ala Ile Val Gln Arg Pro Arg Glu Leu Arg Thr Trp Lys Ala Glu
 145 150 155 160
 Gly Ile Arg Leu Trp Gly Pro
 165

<210> 868
 <211> 28
 <212> PRT
 <213> Homo sapiens

<400> 868
 Leu Gln Val Met Gly Ile Ala Leu Ala Val Leu Gly Trp Leu Ala Val
 1 5 10 15
 Met Leu Cys Cys Ala Leu Pro Met Trp Arg Val Thr
 20 25

<210> 869
 <211> 22
 <212> PRT
 <213> Homo sapiens

<400> 869
 Ser Asn Ile Val Thr Ser Gln Thr Ile Trp Glu Gly Leu Trp Met Asn
 1 5 10 15
 Cys Val Val Gln Ser Thr
 20

<210> 870
 <211> 18
 <212> PRT
 <213> Homo sapiens

<400> 870
 Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp
 1 5 10 15
 Leu Gln

<210> 871
 <211> 18
 <212> PRT
 <213> Homo sapiens

<400> 871
 Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser Ala Lys Ala Lys Thr Met
 1 5 10 15
 Ile Val

459

<210> 872
<211> 32
<212> PRT
<213> Homo sapiens

<400> 872
Gly Val Val Phe Leu Leu Ala Gly Leu Met Val Ile Val Pro Val Ser
1 5 10 15
Trp Thr Ala His Asn Ile Ile Gln Asp Phe Tyr Asn Pro Leu Val Ala
20 25 30

<210> 873
<211> 12
<212> PRT
<213> Homo sapiens

<400> 873
Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro Tyr
1 5 10

<210> 874
<211> 14
<212> PRT
<213> Homo sapiens

<400> 874
Pro Phe Thr Ala Ile Ala Gly Ser Glu Ile Phe Ser Leu Glu
1 5 10

<210> 875
<211> 11
<212> PRT
<213> Homo sapiens

<400> 875
Ser Lys Thr Glu Ala Leu Thr Gln Ala Phe Arg
1 5 10

<210> 876
<211> 24
<212> PRT
<213> Homo sapiens

<400> 876
Val Val His Thr Val Ser Leu His Glu Ile Asp Val Ile Asn Ser Arg
1 5 10 15

460

Thr Gln Gly Phe Leu Ala Leu Phe
20

<210> 877
<211> 15
<212> PRT
<213> Homo sapiens

<400> 877
Pro Gly Val Leu Phe Ile Asp Glu Val His Met Leu Asp Ile Glu
1 5 10 15

<210> 878
<211> 280
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (197)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 878
Ala Gly Ile Arg Gln Arg Phe Ser Ala Arg Leu Trp Gln Leu Val Ser
1 5 10 15
Ile Met Ala Thr Val Thr Ala Thr Thr Lys Val Pro Glu Ile Arg Asp
20 25 30
Val Thr Arg Ile Glu Arg Ile Gly Ala His Ser His Ile Arg Gly Leu
35 40 45
Gly Leu Asp Asp Ala Leu Glu Pro Arg Gln Ala Ser Gln Gly Met Val
50 55 60
Gly Gln Leu Ala Ala Arg Arg Ala Ala Gly Val Val Leu Glu Met Ile
65 70 75 80
Arg Glu Gly Lys Ile Ala Gly Arg Ala Val Leu Ile Ala Gly Gln Pro
85 90 95
Gly Thr Gly Lys Thr Ala Ile Ala Met Gly Met Ala Gln Ala Leu Gly
100 105 110
Pro Asp Thr Pro Phe Thr Ala Ile Ala Gly Ser Glu Ile Phe Ser Leu
115 120 125
Glu Met Ser Lys Thr Glu Ala Leu Thr Gln Ala Phe Arg Arg Ser Ile
130 135 140
Gly Val Arg Ile Lys Glu Glu Thr Glu Ile Ile Glu Gly Glu Val Val
145 150 155 160
Glu Ile Gln Ile Asp Arg Pro Ala Thr Gly Thr Gly Ser Lys Val Gly
165 170 175

461

Lys Leu Thr Leu Lys Thr Thr Glu Met Glu Thr Ile Tyr Asp Leu Gly
 180 185 190
 Thr Lys Met Ile Xaa Ser Leu Thr Lys Asp Lys Val Gln Ala Gly Asp
 195 200 205
 Val Ile Thr Ile Asp Lys Ala Thr Gly Lys Ile Ser Lys Leu Gly Arg
 210 215 220
 Ser Phe Thr Arg Ala Arg Glu Leu Arg Arg Tyr Gly Leu Pro Asp Gln
 225 230 235 240
 Val Arg Ala Val Pro Arg Trp Gly Ala Pro Glu Thr Gln Gly Gly Gly
 245 250 255
 Ala His Arg Val Pro Ala Arg Asp Arg Arg His Gln Leu Ser His Pro
 260 265 270
 Gly Leu Pro Gly Ala Leu Leu Arg
 275 280

<210> 879

<211> 179

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (178)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 879

Ser Pro Ser Thr Arg Arg Arg Ala Arg Ser Pro Ser Trp Ala Ala Pro
 1 5 10 15

Ser His Ala Pro Ala Asn Tyr Asp Ala Met Gly Ser Gln Thr Lys Phe
 20 25 30

Val Gln Cys Pro Asp Gly Glu Leu Gln Lys Arg Lys Glu Val Val His
 35 40 45

Thr Val Ser Leu His Glu Ile Asp Val Ile Asn Ser Arg Thr Gln Gly
 50 55 60

Phe Leu Ala Leu Phe Ser Gly Asp Thr Gly Glu Ile Lys Ser Glu Val
 65 70 75 80

Arg Glu Gln Ile Asn Ala Lys Val Ala Glu Trp Arg Glu Glu Gly Lys
 85 90 95

Ala Glu Ile Ile Pro Gly Val Leu Phe Ile Asp Glu Val His Met Leu
 100 105 110

Asp Ile Glu Ser Phe Ser Phe Leu Asn Arg Ala Leu Glu Ser Asp Met
 115 120 125

Ala Pro Val Gln Gln Val Tyr Gly Asp Ala Val Arg Ala Leu Val Ala

462

130 135 140

Gly Ala Pro Asp Ser Arg Asp Ala Thr Val Gly Gly Leu Val Pro Asn
 145 150 155 160

Ser Cys Ser Pro Gly Asp Pro Leu Val Leu Glu Arg Pro Pro Pro Arg
 165 170 175

Trp Xaa Ser

<210> 880
 <211> 89
 <212> PRT
 <213> Homo sapiens

<400> 880

Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Ala Thr Asn Arg Gly
 1 5 10 15

Ile Thr Arg Ile Arg Gly Thr Ser Tyr Gln Ser Pro His Gly Ile Pro
 20 25 30

Ile Asp Leu Leu Asp Arg Arg His Val Thr Leu Gln Gly Pro Val Glu
 35 40 45

Glu Gly Glu Ala Leu Asp Val Gln His Val Asp Leu Val Asp Glu Gln
 50 55 60

His Ser Arg Asp Asp Leu Arg Leu Ala Leu Leu Ala Pro Leu Ser His
 65 70 75 80

Leu Gly Ile Asp Leu Leu Thr Asp Phe
 85

<210> 881
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 881

Tyr Asp Ala Met Gly Ser Gln Thr Lys Phe Val Gln Cys Pro Asp Gly
 1 5 10 15

Glu Leu Gln Lys Arg Lys Glu Val Val His Thr Val Ser Leu
 20 25 30

<210> 882
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 882

Lys Ala Glu Ile Ile Pro Gly Val Leu Phe Ile Asp Glu Val His Met
 1 5 10 15

463

Leu Asp Ile Glu Ser Phe Ser Phe Leu Asn Arg Ala Leu Glu Ser
20 25 30

<210> 883
<211> 28
<212> PRT
<213> Homo sapiens

<400> 883
Glu Ala Thr Asn Arg Gly Ile Thr Arg Ile Arg Gly Thr Ser Tyr Gln
1 5 10 15

Ser Pro His Gly Ile Pro Ile Asp Leu Leu Asp Arg
20 25

<210> 884
<211> 22
<212> PRT
<213> Homo sapiens

<400> 884
Met Arg Ser Ala Arg Pro Ser Leu Gly Cys Leu Pro Ser Trp Ala Phe
1 5 10 15

Ser Gln Ala Leu Asn Ile
20

<210> 885
<211> 22
<212> PRT
<213> Homo sapiens

<400> 885
Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys
1 5 10 15

Glu Lys Gly Asn Phe Asn
20

<210> 886
<211> 26
<212> PRT
<213> Homo sapiens

<400> 886
Val Ala His Gly Leu Ala Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu
1 5 10 15

Ile Leu Pro Glu Leu Gln Ala Arg Ile Arg
20 25

<210> 887

464

<211> 18
 <212> PRT
 <213> Homo sapiens

<400> 887
 Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln
 1 5 10 15

Arg Cys

<210> 888
 <211> 43
 <212> PRT
 <213> Homo sapiens

<400> 888
 Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met Ala
 1 5 10 15

Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly Asp
 20 25 30

Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn
 35 40

<210> 889
 <211> 45
 <212> PRT
 <213> Homo sapiens

<400> 889
 Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr Cys Val
 1 5 10 15

Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser Gln Tyr
 20 25 30

Ser Gln Ala Gly Phe Ser Gly Glu Asp Arg Leu Glu Gln
 35 40 45

<210> 890
 <211> 92
 <212> PRT
 <213> Homo sapiens

<400> 890
 Ala Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro
 1 5 10 15

Glu Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp
 20 25 30

Asp Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln
 35 40 45

465

Glu Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val
 50 55 60

Pro Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ile Ser Gly
 65 70 75 80

Met Glu Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser
 85 90

<210> 891

<211> 43

<212> PRT

<213> Homo sapiens

<400> 891

Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys
 1 5 10 15

Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala Trp Ser Tyr Tyr
 20 25 30

Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu
 35 40

<210> 892

<211> 76

<212> PRT

<213> Homo sapiens

<400> 892

Leu Arg Leu His Ser Glu Lys Leu Pro Leu Ala Ala Arg Ser Ala Gly
 1 5 10 15

Pro Ser Leu Leu Val Ile Ile Gln Ser Ser Gln Cys Pro Gly Gly Arg
 20 25 30

Arg Tyr Arg Gly Ser Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys
 35 40 45

Pro Leu Arg Arg Gly Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr
 50 55 60

Ser Leu Pro Asn Ala Val Gly Pro Pro Phe Thr Trp
 65 70 75

<210> 893

<211> 133

<212> PRT

<213> Homo sapiens

<400> 893

Val Trp Leu Thr Pro Thr Phe Ala Ser Trp Ile Asn Cys Pro Ser Arg
 1 5 10 15

466

Pro Val Thr Val Leu Ala Ser Arg Ile Gly Phe Thr Ala Thr Ala Ser
 20 25 30

Met Ser Phe Trp Arg Thr Gly Ser Gly Arg Ala Pro Val Ser Trp Ser
 35 40 45

Thr Pro Pro Pro Cys Arg Leu Cys Leu Pro Cys His Asn Thr Val Lys
 50 55 60

Leu Ala Leu Ala Gly Arg Ile Gly Leu Ser Arg Pro Asn Ser Ser Ala
 65 70 75 80

Gly His Leu Arg Thr Ser Trp Gln Met Pro Leu Ser Leu Arg Thr Thr
 85 90 95

Ala Ala Ser Leu Pro Thr Arg Asn Leu Gln Met Thr Ala Ala Ser Arg
 100 105 110

Cys Pro Arg Arg Phe Ser Gly Thr Cys Gly Arg Arg Lys Arg Lys Arg
 115 120 125

Leu Leu Trp Ala Ala
 130

<210> 894
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 894
 Gly Val Cys Gln Val Ser Phe Met Gly Pro Ser Arg Pro Thr Pro His
 1 5 10 15

Pro Ser Pro Leu Pro Leu Pro Gly Asp Ala Glu Leu Ser Gln Trp Tyr
 20 25 30

Gln Gln Ala Pro Ser Pro Ser Gly Ser Trp Ser Cys Ser Ile Ile Gly
 35 40 45

Glu Pro Gln Gln Lys Asn Gly Glu Glu Glu Glu Ala Glu Phe Gly Val
 50 55 60

Leu Asn Pro Pro Ala Pro Thr Leu Gln His Gln Gly Cys Tyr Gly Leu
 65 70 75 80

Ser Cys Arg Ala Thr Leu Ala
 85

<210> 895
 <211> 22
 <212> PRT
 <213> Homo sapiens

<400> 895
 Thr Met Lys Leu Leu Lys Leu Arg Arg Asn Ile Val Lys Leu Ser Leu
 1 5 10 15

467

Tyr Arg His Phe Thr Asn
20

<210> 896
<211> 22
<212> PRT
<213> Homo sapiens

<400> 896
Thr Leu Ile Leu Ala Val Ala Ala Ser Ile Val Phe Ile Ile Trp Thr
1 5 10 15

Thr Met Lys Phe Arg Ile
20

<210> 897
<211> 28
<212> PRT
<213> Homo sapiens

<400> 897
Val Thr Cys Gln Ser Asp Trp Arg Glu Leu Trp Val Asp Asp Ala Ile
1 5 10 15

Trp Arg Leu Leu Phe Ser Met Ile Leu Phe Val Ile
20 25

<210> 898
<211> 27
<212> PRT
<213> Homo sapiens

<400> 898
Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln Arg Phe Ala Phe Ser
1 5 10 15

Pro Leu Ser Glu Glu Glu Glu Asp Glu Gln
20 25

<210> 899
<211> 27
<212> PRT
<213> Homo sapiens

<400> 899
Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln Arg Phe Ala Phe Ser
1 5 10 15

Pro Leu Ser Glu Glu Glu Glu Asp Glu Gln
20 25

<210> 900

468

<211> 35
<212> PRT
<213> Homo sapiens

<400> 900
Lys Glu Pro Met Leu Lys Glu Ser Phe Glu Gly Met Lys Met Arg Ser
1 5 10 15
Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys Val Asn Lys Ala Gln Glu
20 25 30
Asp Asp Leu
35

<210> 901
<211> 37
<212> PRT
<213> Homo sapiens

<400> 901
Lys Trp Val Glu Glu Asn Val Pro Ser Ser Val Thr Asp Val Ala Leu
1 5 10 15
Pro Ala Leu Leu Asp Ser Asp Glu Glu Arg Met Ile Thr His Phe Glu
20 25 30
Arg Ser Lys Met Glu
35

<210> 902
<211> 20
<212> PRT
<213> Homo sapiens

<400> 902
Asp Pro Arg Val Arg Leu Asn Ser Leu Thr Cys Lys His Ile Phe Ile
1 5 10 15
Ser Leu Thr Gln
20

<210> 903
<211> 11
<212> PRT
<213> Homo sapiens

<400> 903
Asn Ala Phe Gly Arg His Ser Thr Ala Val Lys
1 5 10

<210> 904
<211> 283
<212> PRT
<213> Homo sapiens

469

<220>

<221> SITE

<222> (16)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (65)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 904

Glu	Ser	Cys	Leu	Leu	Cys	Gly	Ile	Ser	Glu	Tyr	Pro	Ile	Gln	Arg	Xaa
1				5					10					15	

Ile	Cys	Pro	Gly	Cys	Phe	Asp	Pro	Cys	Arg	Xaa	Ala	Phe	Ser	Ser	Glu
			20					25					30		

Thr	Leu	Thr	Gly	Ser	Asn	Pro	Gly	His	His	Ser	Gln	Ser	Gly	Ile	Trp
		35					40					45			

His	Arg	Gln	Ala	Thr	Pro	Gly	Val	Thr	Leu	His	Lys	Val	Val	Val	Ala
	50					55					60				

Xaa	Ala	Leu	Tyr	Leu	Leu	Phe	Ser	Gly	Met	Glu	Gly	Val	Leu	Arg	Val
65					70					75					80

Thr	Gly	Ala	Gln	Thr	Asp	Leu	Ala	Ser	Leu	Ala	Phe	Ile	Pro	Leu	Ala
				85					90					95	

Phe	Leu	Asp	Thr	Ala	Leu	Cys	Trp	Trp	Ile	Phe	Ile	Ser	Leu	Thr	Gln
			100					105					110		

Thr	Met	Lys	Leu	Leu	Lys	Leu	Arg	Arg	Asn	Ile	Val	Lys	Leu	Ser	Leu
		115					120					125			

Tyr	Arg	His	Phe	Thr	Asn	Thr	Leu	Ile	Leu	Ala	Val	Ala	Ala	Ser	Ile
	130					135					140				

Val	Phe	Ile	Ile	Trp	Thr	Thr	Met	Lys	Phe	Arg	Ile	Val	Thr	Cys	Gln
145					150					155					160

Ser	Asp	Trp	Arg	Glu	Leu	Trp	Val	Asp	Asp	Ala	Ile	Trp	Arg	Leu	Leu
				165					170					175	

Phe	Ser	Met	Ile	Leu	Phe	Val	Ile	Met	Val	Leu	Trp	Arg	Pro	Ser	Ala
			180					185						190	

Asn	Asn	Gln	Arg	Phe	Ala	Phe	Ser	Pro	Leu	Ser	Glu	Glu	Glu	Glu	Glu
		195					200					205			

Asp	Glu	Gln	Lys	Glu	Pro	Met	Leu	Lys	Glu	Ser	Phe	Glu	Gly	Met	Lys
	210					215					220				

470

Met Arg Ser Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys Val Asn Lys
 225 230 235 240

Ala Gln Glu Asp Asp Leu Lys Trp Val Glu Glu Asn Val Pro Ser Ser
 245 250 255

Val Thr Asp Val Ala Leu Pro Ala Leu Leu Asp Ser Asp Glu Glu Arg
 260 265 270

Met Ile Thr His Phe Glu Arg Ser Lys Met Glu
 275 280

<210> 905

<211> 13

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 905

Tyr Glu Pro Met Asp Phe Xaa Met Ala Leu Ile Tyr Asp
 1 5 10

<210> 906

<211> 16

<212> PRT

<213> Homo sapiens

<400> 906

Ile Arg His Glu Leu Thr Val Leu Arg Asp Thr Arg Pro Ala Cys Ala
 1 5 10 15

<210> 907

<211> 10

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 907

Met Asp Phe Xaa Met Ala Leu Ile Tyr Asp
 1 5 10

<210> 908

471

<211> 24
 <212> PRT
 <213> Homo sapiens

<400> 908
 Met Gln Glu Met Met Arg Asn Gln Asp Arg Ala Leu Ser Asn Leu Glu
 1 5 10 15
 Ser Ile Pro Gly Gly Tyr Asn Ala
 20

<210> 909
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 909
 Leu Arg Arg Met Tyr Thr Asp Ile Gln Glu Pro Met Leu Ser Ala Ala
 1 5 10 15
 Gln Glu Gln Phe Gly Gly Asn Pro Phe
 20 25

<210> 910
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 910
 Ala Ser Leu Val Ser Asn Thr Ser Ser Gly Glu Gly Ser Gln Pro Ser
 1 5 10 15
 Arg Thr Glu Asn Arg Asp Pro Leu Pro Asn Pro Trp Ala Pro Gln Thr
 20 25 30

<210> 911
 <211> 71
 <212> PRT
 <213> Homo sapiens

<400> 911
 Ser Gln Ser Ser Ser Ala Ser Ser Gly Thr Ala Ser Thr Val Gly Gly
 1 5 10 15
 Thr Thr Gly Ser Thr Ala Ser Gly Thr Ser Gly Gln Ser Thr Thr Ala
 20 25 30
 Pro Asn Leu Val Pro Gly Val Gly Ala Ser Met Phe Asn Thr Pro Gly
 35 40 45
 Met Gln Ser Leu Leu Gln Gln Ile Thr Glu Asn Pro Gln Leu Met Gln
 50 55 60

472

Asn Met Leu Ser Ala Pro Tyr
65 70

<210> 912
<211> 45
<212> PRT
<213> Homo sapiens

<400> 912
Met Arg Ser Met Met Gln Ser Leu Ser Gln Asn Pro Asp Leu Ala Ala
1 5 10 15

Gln Met Met Leu Asn Asn Pro Leu Phe Ala Gly Asn Pro Gln Leu Gln
20 25 30

Glu Gln Met Arg Gln Gln Leu Pro Thr Phe Leu Gln Gln
35 40 45

<210> 913
<211> 73
<212> PRT
<213> Homo sapiens

<400> 913
Met Gln Asn Pro Asp Thr Leu Ser Ala Met Ser Asn Pro Arg Ala Met
1 5 10 15

Gln Ala Leu Leu Gln Ile Gln Gln Gly Leu Gln Thr Leu Ala Thr Glu
20 25 30

Ala Pro Gly Leu Ile Pro Gly Phe Thr Pro Gly Leu Gly Ala Leu Gly
35 40 45

Ser Thr Gly Gly Ser Ser Gly Thr Asn Gly Ser Asn Ala Thr Pro Ser
50 55 60

Glu Asn Thr Ser Pro Thr Ala Gly Thr
65 70

<210> 914
<211> 72
<212> PRT
<213> Homo sapiens

<400> 914
Thr Glu Pro Gly His Gln Gln Phe Ile Gln Gln Met Leu Gln Ala Leu
1 5 10 15

Ala Gly Val Asn Pro Gln Leu Gln Asn Pro Glu Val Arg Phe Gln Gln
20 25 30

Gln Leu Glu Gln Leu Ser Ala Met Gly Phe Leu Asn Arg Glu Ala Asn
35 40 45

473

Leu Gln Ala Leu Ile Ala Thr Gly Gly Asp Ile Asn Ala Ala Ile Glu
50 55 60

Arg Leu Leu Gly Ser Gln Pro Ser
65 70

<210> 915
<211> 45
<212> PRT
<213> Homo sapiens

<400> 915
Arg Asn Pro Ala Met Met Gln Glu Met Met Arg Asn Gln Asp Arg Ala
1 5 10 15

Leu Ser Asn Leu Glu Ser Ile Pro Gly Gly Tyr Asn Ala Leu Arg Arg
20 25 30

Met Tyr Thr Asp Ile Gln Glu Pro Met Leu Ser Ala Ala
35 40 45

<210> 916
<211> 13
<212> PRT
<213> Homo sapiens

<400> 916
Gly Asn Pro Phe Ala Ser Leu Val Ser Asn Thr Ser Ser
1 5 10

<210> 917
<211> 11
<212> PRT
<213> Homo sapiens

<400> 917
Glu Asn Arg Asp Pro Leu Pro Asn Pro Trp Ala
1 5 10

<210> 918
<211> 17
<212> PRT
<213> Homo sapiens

<400> 918
Gly Lys Ile Leu Lys Asp Gln Asp Thr Leu Ser Gln His Gly Ile His
1 5 10 15

Asp

<210> 919
<211> 14

474

<212> PRT

<213> Homo sapiens

<400> 919

Gly Leu Thr Val His Leu Val Ile Lys Thr Gln Asn Arg Pro
1 5 10

<210> 920

<211> 18

<212> PRT

<213> Homo sapiens

<400> 920

Ser Glu Leu Gln Ser Gln Met Gln Arg Gln Leu Leu Ser Asn Pro Glu
1 5 10 15

Met Met

<210> 921

<211> 14

<212> PRT

<213> Homo sapiens

<400> 921

Pro Glu Ile Ser His Met Leu Asn Asn Pro Asp Ile Met Arg
1 5 10

<210> 922

<211> 18

<212> PRT

<213> Homo sapiens

<400> 922

Arg Gln Leu Ile Met Ala Asn Pro Gln Met Gln Gln Leu Ile Gln Arg
1 5 10 15

Asn Pro

<210> 923

<211> 27

<212> PRT

<213> Homo sapiens

<400> 923

Asn Leu Cys His Val Asp Cys Gln Asp Leu Leu Asn Pro Asn Leu Leu
1 5 10 15

Ala Gly Ile His Cys Ala Lys Arg Ile Val Ser
20 25

<210> 924

475

<211> 23
<212> PRT
<213> Homo sapiens

<400> 924
Leu Asp Gly Phe Glu Gly Tyr Ser Leu Ser Asp Trp Leu Cys Leu Ala
1 5 10 15
Phe Val Glu Ser Lys Phe Asn
20

<210> 925
<211> 22
<212> PRT
<213> Homo sapiens

<400> 925
Asn Glu Asn Ala Asp Gly Ser Phe Asp Tyr Gly Leu Phe Gln Ile Asn
1 5 10 15
Ser His Tyr Trp Cys Asn
20

<210> 926
<211> 27
<212> PRT
<213> Homo sapiens

<400> 926
Asn Leu Cys His Val Asp Cys Gln Asp Leu Leu Asn Pro Asn Leu Leu
1 5 10 15
Ala Gly Ile His Cys Ala Lys Arg Ile Val Ser
20 25

<210> 927
<211> 13
<212> PRT
<213> Homo sapiens

<400> 927
Glu Pro Ser Ala Leu Ser Cys Thr Ser Ser Pro Pro Arg
1 5 10

<210> 928
<211> 13
<212> PRT
<213> Homo sapiens

<400> 928
Ile Arg Glu Val Asn Glu Val Ile Gln Asn Pro Ala Thr
1 5 10

476

<210> 929
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 929
 Ile Thr Arg Ile Leu Leu Ser His Phe Asn Trp Asp Lys Glu Lys Leu
 1 5 10 15
 Met Glu Arg Tyr Phe Asp Gly Asn Leu Glu Lys Leu Phe Ala
 20 25 30

<210> 930
 <211> 23
 <212> PRT
 <213> Homo sapiens

<400> 930
 Asn Thr Arg Ser Ser Ala Gln Asp Met Pro Cys Gln Ile Cys Tyr Leu
 1 5 10 15
 Asn Tyr Pro Asn Ser Tyr Phe
 20

<210> 931
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 931
 Cys Asp Ile Leu Val Asp Asp Asn Thr Val Met Arg Leu Ile Thr Asp
 1 5 10 15
 Ser Lys Val Lys Leu Lys Tyr Gln His Leu Ile Thr Asn Ser Phe Val
 20 25 30
 Glu Cys Asn Arg Leu Leu Lys Trp Cys Pro Ala Pro Asp Cys His His
 35 40 45
 Val Val Lys Val Gln Tyr Pro Asp Ala Lys Pro Val
 50 55 60

<210> 932
 <211> 52
 <212> PRT
 <213> Homo sapiens

<400> 932
 Cys Asp Ile Leu Val Asp Asp Asn Thr Val Met Arg Leu Ile Thr Asp
 1 5 10 15
 Ser Lys Val Lys Leu Lys Tyr Gln His Leu Ile Thr Asn Ser Phe Val
 20 25 30
 Glu Cys Asn Arg Leu Leu Lys Trp Cys Pro Ala Pro Asp Cys His His

477

35

40

45

Val Val Lys Val
50

<210> 933

<211> 60

<212> PRT

<213> Homo sapiens

<400> 933

Gly Cys Asn His Met Val Cys Arg Asn Gln Asn Cys Lys Ala Glu Phe
1 5 10 15

Cys Trp Val Cys Leu Gly Pro Trp Glu Pro His Gly Ser Ala Trp Tyr
20 25 30

Asn Cys Asn Arg Tyr Asn Glu Asp Asp Ala Lys Ala Ala Arg Asp Ala
35 40 45

Gln Glu Arg Ser Arg Ala Ala Leu Gln Arg Tyr Leu
50 55 60

<210> 934

<211> 60

<212> PRT

<213> Homo sapiens

<400> 934

Phe Tyr Cys Asn Arg Tyr Met Asn His Met Gln Ser Leu Arg Phe Glu
1 5 10 15

His Lys Leu Tyr Ala Gln Val Lys Gln Lys Met Glu Glu Met Gln Gln
20 25 30

His Asn Met Ser Trp Ile Glu Val Gln Phe Leu Lys Lys Ala Val Asp
35 40 45

Val Leu Cys Gln Cys Arg Ala Thr Leu Met Tyr Thr
50 55 60

<210> 935

<211> 60

<212> PRT

<213> Homo sapiens

<400> 935

Tyr Val Phe Ala Phe Tyr Leu Lys Lys Asn Asn Gln Ser Ile Ile Phe
1 5 10 15

Glu Asn Asn Gln Ala Asp Leu Glu Asn Ala Thr Glu Val Leu Ser Gly
20 25 30

Tyr Leu Glu Arg Asp Ile Ser Gln Asp Ser Leu Gln Asp Ile Lys Gln
35 40 45

478

Lys Val Gln Asp Lys Tyr Arg Tyr Cys Glu Ser Arg
50 55 60

<210> 936
<211> 37
<212> PRT
<213> Homo sapiens

<400> 936
Thr Gly Leu Glu Cys Gly His Lys Phe Cys Met Gln Cys Trp Ser Glu
1 5 10 15
Tyr Leu Thr Thr Lys Ile Met Glu Glu Gly Met Gly Gln Thr Ile Ser
20 25 30

Cys Pro Ala His Gly
35

<210> 937
<211> 21
<212> PRT
<213> Homo sapiens

<400> 937
Met Trp Gly Tyr Leu Phe Val Asp Ala Ala Trp Asn Phe Leu Gly Cys
1 5 10 15
Leu Ile Cys Gly Trp
20

<210> 938
<211> 46
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (21)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 938
Met His Phe Ile Ser Ser Gly Asn Val Ser Ala Ile Arg Ser Ser Ile
1 5 10 15
Leu Leu Leu Arg Xaa Ser Leu Ser Tyr Leu Gly Asn Cys Leu Arg Val
20 25 30

Ser Ala Ile Phe Val Tyr Phe Leu Leu Phe Leu Leu Ser
35 40 45

<210> 939
<211> 80
<212> PRT

479

<213> Homo sapiens

<400> 939

Met Asp Gln Ala Leu Arg Gly Ser Pro Ser Glu Gly Phe Ser Thr Asp
 1 5 10 15

Pro Ser Pro Pro Gln Val Gly Arg Gln Ile Pro Ser Phe Pro Pro Trp
 20 25 30

Arg Arg Leu Val Leu Pro Lys Ala Ser Gly Cys Phe Leu Glu Arg Glu
 35 40 45

Trp Trp Leu Cys Val Phe Lys Leu Arg Thr Arg Pro Gly Ala Glu Ala
 50 55 60

His Ala Tyr Asn Ser Ser Ile Leu Gly Gly Arg Gly Lys Gly Ile Thr
 65 70 75 80

<210> 940

<211> 131

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 940

Met Leu Pro Ala Leu Ala Ser Cys Cys His Phe Ser Pro Pro Glu Gln
 1 5 10 15

Ala Ala Arg Leu Lys Lys Leu Gln Glu Gln Glu Lys Gln Gln Lys Val
 20 25 30

Glu Phe Arg Lys Arg Met Glu Lys Glu Val Ser Asp Phe Ile Gln Asp
 35 40 45

Ser Gly Gln Ile Lys Lys Lys Phe Gln Pro Met Asn Lys Ile Glu Arg
 50 55 60

Ser Ile Leu His Asp Val Val Glu Val Ala Gly Leu Thr Ser Phe Ser
 65 70 75 80

Phe Gly Glu Asp Asp Asp Cys Arg Tyr Val Met Ile Phe Lys Lys Glu
 85 90 95

Phe Ala Pro Ser Asp Glu Glu Leu Asp Ser Tyr Arg Arg Gly Glu Glu
 100 105 110

Trp Asp Pro Gln Lys Ala Glu Glu Lys Arg Asn Xaa Lys Glu Leu Ala
 115 120 125

Gln Arg Gln

480

130

<210> 941

<211> 76

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 941

Glu Glu Glu Ala Ala Gln Gln Gly Pro Val Val Val Ser Pro Ala Ser
 1 5 10 15

Asp Tyr Lys Asp Lys Tyr Ser His Leu Ile Gly Lys Gly Ala Ala Lys
 20 25 30

Asp Ala Ala His Met Leu Gln Ala Asn Lys Thr Tyr Gly Cys Xaa Pro
 35 40 45

Val Ala Asn Lys Arg Asp Thr Arg Ser Ile Glu Glu Ala Met Asn Glu
 50 55 60

Ile Arg Ala Lys Lys Arg Leu Arg Gln Ser Gly Glu
 65 70 75

<210> 942

<211> 40

<212> PRT

<213> Homo sapiens

<400> 942

Pro Pro Arg Arg Pro Ala Gln Leu Pro Leu Thr Pro Gly Ala Gly Gln
 1 5 10 15

Gly Ala Gly Arg Asp Lys Ala Ala Ala Ile Arg Ala His Pro Gly Ala
 20 25 30

Pro Pro Leu Asn His Leu Leu Pro
 35 40

<210> 943

<211> 28

<212> PRT

<213> Homo sapiens

<400> 943

Ala Val Pro Gln Ala Gly Gly Lys Gln Val Phe Asp Leu Ser Pro Leu
 1 5 10 15

Glu Leu Gly Tyr Val Arg Gly Met Cys Val Cys Val
 20 25

481

<210> 944
 <211> 207
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (124)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (178)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 944
 Met Leu Pro Ala Leu Ala Ser Cys Cys His Phe Ser Pro Pro Glu Gln
 1 5 10 15

Ala Ala Arg Leu Lys Lys Leu Gln Glu Gln Glu Lys Gln Gln Lys Val
 20 25 30

Glu Phe Arg Lys Arg Met Glu Lys Glu Val Ser Asp Phe Ile Gln Asp
 35 40 45

Ser Gly Gln Ile Lys Lys Lys Phe Gln Pro Met Asn Lys Ile Glu Arg
 50 55 60

Ser Ile Leu His Asp Val Val Glu Val Ala Gly Leu Thr Ser Phe Ser
 65 70 75 80

Phe Gly Glu Asp Asp Asp Cys Arg Tyr Val Met Ile Phe Lys Lys Glu
 85 90 95

Phe Ala Pro Ser Asp Glu Glu Leu Asp Ser Tyr Arg Arg Gly Glu Glu
 100 105 110

Trp Asp Pro Gln Lys Ala Glu Glu Lys Arg Asn Xaa Lys Glu Leu Ala
 115 120 125

Gln Arg Gln Glu Glu Glu Ala Ala Gln Gln Gly Pro Val Val Val Ser
 130 135 140

Pro Ala Ser Asp Tyr Lys Asp Lys Tyr Ser His Leu Ile Gly Lys Gly
 145 150 155 160

Ala Ala Lys Asp Ala Ala His Met Leu Gln Ala Asn Lys Thr Tyr Gly
 165 170 175

Cys Xaa Pro Val Ala Asn Lys Arg Asp Thr Arg Ser Ile Glu Glu Ala
 180 185 190

Met Asn Glu Ile Arg Ala Lys Lys Arg Leu Arg Gln Ser Gly Glu
 195 200 205

<210> 945

482

<211> 34
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (10)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 945
 Leu Leu Cys Pro Val Leu Asn Ser Gly Xaa Ser Trp Asn Phe Pro His
 1 5 10 15
 Pro Ser Gln Pro Glu Tyr Ser Phe His Gly Phe His Ser Thr Arg Leu
 20 25 30
 Trp Ile

<210> 946
 <211> 28
 <212> PRT
 <213> Homo sapiens

<400> 946
 Pro Ser Thr Pro Trp Phe Leu Phe Leu Leu Gly Leu Thr Cys Pro Phe
 1 5 10 15
 Ser Thr Ser His Pro Arg Trp Asp Ser Ile Pro Pro
 20 25

<210> 947
 <211> 227
 <212> PRT
 <213> Homo sapiens

<400> 947
 Glu Leu Ser Ile Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu
 1 5 10 15
 Tyr Thr Cys Ser Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu
 20 25 30
 Val Thr Val Leu Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys
 35 40 45
 Ser Ser Leu Arg Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser
 50 55 60
 Gly Ser Lys Pro Ala Ala Arg Leu Thr Trp Arg Lys Gly Asp Gln Glu
 65 70 75 80
 Leu His Gly Glu Pro Thr Arg Ile Gln Glu Asp Pro Asn Gly Lys Thr
 85 90 95
 Phe Thr Val Ser Ser Ser Val Thr Phe Gln Val Thr Arg Glu Asp Asp

483

100	105	110
Gly Ala Ser Ile Val Cys Ser Val Asn His Glu Ser Leu Lys Gly Ala		
115	120	125
Asp Arg Ser Thr Ser Gln Arg Ile Glu Val Leu Tyr Thr Pro Thr Ala		
130	135	140
Met Ile Arg Pro Asp Pro Pro His Pro Arg Glu Gly Gln Lys Leu Leu		
145	150	155
Leu His Cys Glu Gly Arg Gly Asn Pro Val Pro Gln Gln Tyr Leu Trp		
165	170	175
Glu Lys Glu Gly Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser Ala		
180	185	190
Leu Ile Phe Pro Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly Cys		
195	200	205
Thr Ala Thr Ser Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu Asn		
210	215	220
Val Asn Asp		
225		

<210> 948

<211> 64

<212> PRT

<213> Homo sapiens

<400> 948

Glu Leu Ser Ile Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu		
1	5	10
		15
Tyr Thr Cys Ser Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu		
20	25	30
Val Thr Val Leu Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys		
35	40	45
Ser Ser Leu Arg Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser		
50	55	60

<210> 949

<211> 65

<212> PRT

<213> Homo sapiens

<400> 949

Cys Gln Ser Ser Gly Ser Lys Pro Ala Ala Arg Leu Thr Trp Arg Lys		
1	5	10
		15

484

Gly Asp Gln Glu Leu His Gly Glu Pro Thr Arg Ile Gln Glu Asp Pro
 20 25 30

Asn Gly Lys Thr Phe Thr Val Ser Ser Ser Val Thr Phe Gln Val Thr
 35 40 45

Arg Glu Asp Asp Gly Ala Ser Ile Val Cys Ser Val Asn His Glu Ser
 50 55 60

Leu
 65

<210> 950
 <211> 58
 <212> PRT
 <213> Homo sapiens

<400> 950
 His Glu Ser Leu Lys Gly Ala Asp Arg Ser Thr Ser Gln Arg Ile Glu
 1 5 10 15

Val Leu Tyr Thr Pro Thr Ala Met Ile Arg Pro Asp Pro Pro His Pro
 20 25 30

Arg Glu Gly Gln Lys Leu Leu Leu His Cys Glu Gly Arg Gly Asn Pro
 35 40 45

Val Pro Gln Gln Tyr Leu Trp Glu Lys Glu
 50 55

<210> 951
 <211> 52
 <212> PRT
 <213> Homo sapiens

<400> 951
 Trp Glu Lys Glu Gly Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser
 1 5 10 15

Ala Leu Ile Phe Pro Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly
 20 25 30

Cys Thr Ala Thr Ser Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu
 35 40 45

Asn Val Asn Asp
 50

<210> 952
 <211> 36
 <212> PRT
 <213> Homo sapiens

<400> 952
 Pro Ser Pro Val Pro Ser Ser Ser Ser Thr Tyr His Ala Ile Ile Gly

485

1 5 10 15
 Gly Ile Val Ala Phe Ile Val Phe Leu Leu Leu Ile Met Leu Ile Phe
 20 25 30
 Leu Gly His Tyr
 35

<210> 953
 <211> 44
 <212> PRT
 <213> Homo sapiens

<400> 953
 Leu Ile Arg His Lys Gly Thr Tyr Leu Thr His Glu Ala Lys Gly Ser
 1 5 10 15
 Asp Asp Ala Pro Asp Ala Asp Thr Ala Ile Ile Asn Ala Glu Gly Gly
 20 25 30
 Gln Ser Gly Gly Asp Asp Lys Lys Glu Tyr Phe Ile
 35 40

<210> 954
 <211> 123
 <212> PRT
 <213> Homo sapiens

<400> 954
 Val Pro Glu Leu Pro Asp Arg Val His Gln Leu His Gln Ala Val Gln
 1 5 10 15
 Gly Cys Ala Leu Gly Arg Pro Gly Phe Pro Gly Gly Pro Thr His Ser
 20 25 30
 Gly His His Lys Ser His Pro Gly Pro Ala Gly Gly Asp Tyr Asn Arg
 35 40 45
 Cys Asp Arg Pro Gly Gln Val His Leu His Asn Pro Arg Gly Thr Gly
 50 55 60
 Arg Arg Gly Gln Leu His Pro Thr Ala Gly Pro Gly Val His Arg Arg
 65 70 75 80
 Ala Cys Pro Ser Gln Gln Leu Pro His Arg Leu Gly Pro Gly Val Pro
 85 90 95
 Cys Pro Ser Pro Ser Leu Thr Pro Val Leu Pro Ser Trp Thr Gln Ser
 100 105 110
 Trp Cys Gly Leu Pro Gly Tyr Thr Ser Ser Ser
 115 120

<210> 955
 <211> 22

486

<212> PRT

<213> Homo sapiens

<400> 955

Val His Gln Leu His Gln Ala Val Gln Gly Cys Ala Leu Gly Arg Pro
1 5 10 15

Gly Phe Pro Gly Gly Pro
20

<210> 956

<211> 42

<212> PRT

<213> Homo sapiens

<400> 956

Pro Thr His Ser Gly His His Lys Ser His Pro Gly Pro Ala Gly Gly
1 5 10 15

Asp Tyr Asn Arg Cys Asp Arg Pro Gly Gln Val His Leu His Asn Pro
20 25 30

Arg Gly Thr Gly Arg Arg Gly Gln Leu His
35 40

<210> 957

<211> 55

<212> PRT

<213> Homo sapiens

<400> 957

Leu His Pro Thr Ala Gly Pro Gly Val His Arg Arg Ala Cys Pro Ser
1 5 10 15

Gln Gln Leu Pro His Arg Leu Gly Pro Gly Val Pro Cys Pro Ser Pro
20 25 30

Ser Leu Thr Pro Val Leu Pro Ser Trp Thr Gln Ser Trp Cys Gly Leu
35 40 45

Pro Gly Tyr Thr Ser Ser Ser
50 55

<210> 958

<211> 276

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 958

Ser Leu Arg Arg Pro Arg Ser Ala Ala Xaa Gln Thr Leu Thr Thr Phe

487

1	5	10	15
Leu Ser Ser Val Ser Ser Ala Ser Ser Ser Ala Leu Pro Gly Ser Arg	20	25	30
Glu Pro Cys Asp Pro Arg Ala Pro Pro Pro Pro Arg Ser Gly Ser Ala	35	40	45
Ala Ser Cys Cys Ser Cys Cys Cys Ser Cys Pro Arg Arg Arg Ala Pro	50	55	60
Leu Arg Ser Pro Arg Gly Ser Lys Arg Arg Ile Arg Gln Arg Glu Val	65	70	75
Val Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala Gly Val Pro	85	90	95
Gly Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr Pro Gly	100	105	110
Ile Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg	115	120	125
Glu Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp	130	135	140
Ser Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr	145	150	155
Phe Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly	165	170	175
Ser Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe	180	185	190
Thr Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile	195	200	205
Ile Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile	210	215	220
His Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly	225	230	235
Leu Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys	245	250	255
Gly Asp Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu	260	265	270
Glu Leu Pro Lys	275		

<210> 959

<211> 61

<212> PRT

<213> Homo sapiens

488

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 959

Ser Leu Arg Arg Pro Arg Ser Ala Ala Xaa Gln Thr Leu Thr Thr Phe
 1 5 10 15

Leu Ser Ser Val Ser Ser Ala Ser Ser Ser Ala Leu Pro Gly Ser Arg
 20 25 30

Glu Pro Cys Asp Pro Arg Ala Pro Pro Pro Pro Arg Ser Gly Ser Ala
 35 40 45

Ala Ser Cys Cys Ser Cys Cys Cys Ser Cys Pro Arg Arg
 50 55 60

<210> 960

<211> 52

<212> PRT

<213> Homo sapiens

<400> 960

Arg Ala Pro Leu Arg Ser Pro Arg Gly Ser Lys Arg Arg Ile Arg Gln
 1 5 10 15

Arg Glu Val Val Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala
 20 25 30

Gly Val Pro Gly Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly
 35 40 45

Thr Pro Gly Ile
 50

<210> 961

<211> 52

<212> PRT

<213> Homo sapiens

<400> 961

Thr Pro Gly Ile Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu
 1 5 10 15

Cys Leu Arg Glu Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln
 20 25 30

Cys Ser Trp Ser Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala
 35 40 45

Glu Cys Thr Phe
 50

489

<210> 962

<211> 66

<212> PRT

<213> Homo sapiens

<400> 962

Phe Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly
 1 5 10 15

Ser Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe
 20 25 30

Thr Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile
 35 40 45

Ile Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile
 50 55 60

His Arg
 65

<210> 963

<211> 51

<212> PRT

<213> Homo sapiens

<400> 963

Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu
 1 5 10 15

Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys Gly
 20 25 30

Asp Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu Glu
 35 40 45

Leu Pro Lys
 50

<210> 964

<211> 26

<212> PRT

<213> Homo sapiens

<400> 964

Thr Lys Lys Glu Asn Cys Arg Pro Ala Ser Leu Met Asn Ile Asp Thr
 1 5 10 15

Lys Ile Leu Asn Lys Ile Leu Met Asn Gln
 20 25

<210> 965

<211> 214

<212> PRT

<213> Homo sapiens

<220>
 <221> SITE
 <222> (25)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (26)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (90)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (94)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (105)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (120)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 965
 Met Cys Asn Leu Pro Ile Lys Val Val Cys Arg Ala Asn Ala Glu Tyr
 1 5 10 15

Met Ser Pro Ser Gly Lys Val Pro Xaa Xaa His Val Gly Asn Gln Val
 20 25 30

Val Ser Glu Leu Gly Pro Ile Val Gln Phe Val Lys Ala Lys Gly His
 35 40 45

Ser Leu Ser Asp Gly Leu Glu Glu Val Gln Lys Ala Glu Met Lys Ala
 50 55 60

Tyr Met Glu Leu Val Asn Asn Met Leu Leu Thr Ala Glu Leu Tyr Leu
 65 70 75 80

Gln Trp Cys Asp Glu Ala Thr Val Gly Xaa Ile Thr His Xaa Arg Tyr
 85 90 95

Gly Ser Pro Tyr Pro Trp Pro Leu Xaa His Ile Leu Ala Tyr Gln Lys
 100 105 110

Gln Trp Glu Val Lys Arg Lys Xaa Lys Ala Ile Gly Trp Gly Lys Lys
 115 120 125

Thr Leu Asp Gln Val Leu Glu Asp Val Asp Gln Cys Cys Gln Ala Leu
 130 135 140

491

Ser Gln Arg Leu Gly Thr Gln Pro Tyr Phe Phe Asn Lys Gln Pro Thr
 145 150 155 160

Glu Leu Asp Ala Leu Val Phe Gly His Leu Tyr Thr Ile Leu Thr Thr
 165 170 175

Gln Leu Thr Asn Asp Glu Leu Ser Glu Lys Val Lys Asn Tyr Ser Asn
 180 185 190

Leu Leu Ala Phe Cys Arg Arg Ile Glu Gln His Tyr Phe Glu Asp Arg
 195 200 205

Gly Lys Gly Arg Leu Ser
 210

<210> 966

<211> 44

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (26)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 966

Met Cys Asn Leu Pro Ile Lys Val Val Cys Arg Ala Asn Ala Glu Tyr
 1 5 10 15

Met Ser Pro Ser Gly Lys Val Pro Xaa Xaa His Val Gly Asn Gln Val
 20 25 30

Val Ser Glu Leu Gly Pro Ile Val Gln Phe Val Lys
 35 40

<210> 967

<211> 44

<212> PRT

<213> Homo sapiens

<400> 967

Phe Val Lys Ala Lys Gly His Ser Leu Ser Asp Gly Leu Glu Glu Val
 1 5 10 15

Gln Lys Ala Glu Met Lys Ala Tyr Met Glu Leu Val Asn Asn Met Leu
 20 25 30

Leu Thr Ala Glu Leu Tyr Leu Gln Trp Cys Asp Glu
 35 40

492

<210> 968
 <211> 51
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (11)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (15)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (26)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (41)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 968
 Leu Gln Trp Cys Asp Glu Ala Thr Val Gly Xaa Ile Thr His Xaa Arg
 1 5 10 15
 Tyr Gly Ser Pro Tyr Pro Trp Pro Leu Xaa His Ile Leu Ala Tyr Gln
 20 25 30
 Lys Gln Trp Glu Val Lys Arg Lys Xaa Lys Ala Ile Gly Trp Gly Lys
 35 40 45
 Lys Thr Leu
 50

<210> 969
 <211> 43
 <212> PRT
 <213> Homo sapiens

<400> 969
 Asp Gln Val Leu Glu Asp Val Asp Gln Cys Cys Gln Ala Leu Ser Gln
 1 5 10 15
 Arg Leu Gly Thr Gln Pro Tyr Phe Phe Asn Lys Gln Pro Thr Glu Leu
 20 25 30
 Asp Ala Leu Val Phe Gly His Leu Tyr Thr Ile
 35 40

<210> 970
 <211> 41

493

<212> PRT

<213> Homo sapiens

<400> 970

Leu Thr Thr Gln Leu Thr Asn Asp Glu Leu Ser Glu Lys Val Lys Asn
 1 5 10 15

Tyr Ser Asn Leu Leu Ala Phe Cys Arg Arg Ile Glu Gln His Tyr Phe
 20 25 30

Glu Asp Arg Gly Lys Gly Arg Leu Ser
 35 40

<210> 971

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (3)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 971

Met Xaa Xaa Xaa Asn Ser His Ile Thr Ile Phe Thr Leu Asn Val Asn
 1 5 10 15

Gly Leu Asn Ala Pro Asn Glu Arg His Arg Leu Ala Asn Trp Ile Gln
 20 25 30

Ser Gln Asp Gln Val Cys Cys Ile Gln Glu Thr His Leu Thr Gly Arg
 35 40 45

Asp Thr His Arg Leu Lys Ile Lys Gly Trp Arg Lys Ile Tyr Gln Ala
 50 55 60

Asn Gly Lys Gln Lys Lys
 65 70

<210> 972

<211> 28

<212> PRT

<213> Homo sapiens

<400> 972

Phe Thr Leu Asn Val Asn Gly Leu Asn Ala Pro Asn Glu Arg His Arg

494

1 5 10 15
 Leu Ala Asn Trp Ile Gln Ser Gln Asp Gln Val Cys
 20 25

 <210> 973
 <211> 17
 <212> PRT
 <213> Homo sapiens

 <400> 973
 Thr His Leu Thr Gly Arg Asp Thr His Arg Leu Lys Ile Lys Gly Trp
 1 5 10 15
 Arg

 <210> 974
 <211> 14
 <212> PRT
 <213> Homo sapiens

 <400> 974
 Gly Trp Arg Lys Ile Tyr Gln Ala Asn Gly Lys Gln Lys Lys
 1 5 10

 <210> 975
 <211> 54
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 975
 Ile Tyr His Leu His Ser Trp Ile Phe Phe His Phe Lys Arg Ala Phe
 1 5 10 15
 Cys Met Cys Phe Ile Thr Met Lys Val Ile His Ala His Cys Ser Lys
 20 25 30
 Leu Arg Lys Cys Xaa Asn Ala Gln Ile Ser Val Phe Cys Thr Thr Leu
 35 40 45
 Thr Ala Ser Tyr Pro Thr
 50

<210> 976
 <211> 23
 <212> PRT
 <213> Homo sapiens

495

<400> 976

Ile Tyr His Leu His Ser Trp Ile Phe Phe His Phe Lys Arg Ala Phe
 1 5 10 15

Cys Met Cys Phe Ile Thr Met
 20

<210> 977

<211> 31

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 977

Lys Val Ile His Ala His Cys Ser Lys Leu Arg Lys Cys Xaa Asn Ala
 1 5 10 15

Gln Ile Ser Val Phe Cys Thr Thr Leu Thr Ala Ser Tyr Pro Thr
 20 25 30

<210> 978

<211> 58

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (29)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 978

Trp Asn Leu Leu Trp Tyr Phe Gln Arg Leu Arg Leu Pro Ser Ile Leu
 1 5 10 15

Pro Gly Leu Val Leu Ala Ser Cys Asp Gly Pro Ser Xaa Ser Gln Ala
 20 25 30

Pro Ser Pro Trp Leu Thr Pro Asp Pro Ala Ser Val Gln Val Arg Leu
 35 40 45

Leu Trp Asp Val Leu Thr Pro Asp Pro Asn
 50 55

<210> 979

<211> 54

<212> PRT

<213> Homo sapiens

<400> 979

Gln Arg Gly Ile Tyr Arg Glu Ile Leu Phe Leu Thr Met Ala Ala Leu
 1 5 10 15

496

Gly Lys Asp His Val Asp Ile Val Ala Phe Asp Lys Lys Tyr Lys Ser
 20 25 30
 Ala Phe Asn Lys Leu Ala Ser Ser Met Gly Lys Glu Glu Leu Arg His
 35 40 45
 Arg Arg Ala Gln Met Pro
 50

<210> 980
 <211> 23
 <212> PRT
 <213> Homo sapiens

<400> 980
 Trp Asn Leu Leu Trp Tyr Phe Gln Arg Leu Arg Leu Pro Ser Ile Leu
 1 5 10 15
 Pro Gly Leu Val Leu Ala Ser
 20

<210> 981
 <211> 191
 <212> PRT
 <213> Homo sapiens

<400> 981
 Glu Asp Asp Gly Phe Asn Arg Ser Ile His Glu Val Ile Leu Lys Asn
 1 5 10 15
 Ile Thr Trp Tyr Ser Glu Arg Val Leu Thr Glu Ile Ser Leu Gly Ser
 20 25 30
 Leu Leu Ile Leu Val Val Ile Arg Thr Ile Gln Tyr Asn Met Thr Arg
 35 40 45
 Thr Arg Asp Lys Tyr Leu His Thr Asn Cys Leu Ala Ala Leu Ala Asn
 50 55 60
 Met Ser Ala Gln Phe Arg Ser Leu His Gln Tyr Ala Ala Gln Arg Ile
 65 70 75 80
 Ile Ser Leu Phe Ser Leu Leu Ser Lys Lys His Asn Lys Val Leu Glu
 85 90 95
 Gln Ala Thr Gln Ser Leu Arg Gly Ser Leu Ser Ser Asn Asp Val Pro
 100 105 110
 Leu Pro Asp Tyr Ala Gln Asp Leu Asn Val Ile Glu Glu Val Ile Arg
 115 120 125
 Met Met Leu Glu Ile Ile Asn Ser Cys Leu Thr Asn Ser Leu His His
 130 135 140
 Asn Pro Asn Leu Val Tyr Ala Leu Leu Tyr Lys Arg Asp Leu Phe Glu

497

145 150 155 160
 Gln Phe Arg Thr His Pro Ser Phe Gln Asp Ile Met Gln Asn Ile Asp
 165 170 175
 Leu Val Ile Ser Phe Phe Ser Ser Arg Leu Leu Gln Ala Gly Ser
 180 185 190

<210> 982
 <211> 38
 <212> PRT
 <213> Homo sapiens

<400> 982
 Glu Asp Asp Gly Phe Asn Arg Ser Ile His Glu Val Ile Leu Lys Asn
 1 5 10 15
 Ile Thr Trp Tyr Ser Glu Arg Val Leu Thr Glu Ile Ser Leu Gly Ser
 20 25 30
 Leu Leu Ile Leu Val Val
 35

<210> 983
 <211> 53
 <212> PRT
 <213> Homo sapiens

<400> 983
 Arg Thr Ile Gln Tyr Asn Met Thr Arg Thr Arg Asp Lys Tyr Leu His
 1 5 10 15
 Thr Asn Cys Leu Ala Ala Leu Ala Asn Met Ser Ala Gln Phe Arg Ser
 20 25 30
 Leu His Gln Tyr Ala Ala Gln Arg Ile Ile Ser Leu Phe Ser Leu Leu
 35 40 45
 Ser Lys Lys His Asn
 50

<210> 984
 <211> 56
 <212> PRT
 <213> Homo sapiens

<400> 984
 Ser Cys Leu Thr Asn Ser Leu His His Asn Pro Asn Leu Val Tyr Ala
 1 5 10 15
 Leu Leu Tyr Lys Arg Asp Leu Phe Glu Gln Phe Arg Thr His Pro Ser
 20 25 30
 Phe Gln Asp Ile Met Gln Asn Ile Asp Leu Val Ile Ser Phe Phe Ser
 35 40 45

498

Ser Arg Leu Leu Gln Ala Gly Ser
 50 55

<210> 985
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 985
 Lys Lys His Asn Lys Val Leu Glu Gln Ala Thr Gln Ser Leu Arg Gly
 1 5 10 15

Ser Leu Ser Ser Asn Asp Val Pro Leu Pro Asp Tyr Ala Gln Asp
 20 25 30

<210> 986
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 986
 Thr Ile Ser Asn Ser Ser Phe Ile Ser Gly Tyr Asn Ala Lys Tyr
 1 5 10 15

<210> 987
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 987
 Leu Lys Val Ala Ala Ser Trp Glu Leu Ser Cys Gln Trp Asn Gly Ser
 1 5 10 15

Trp Lys Ser Leu Ser Lys Ala Ser Leu Arg Cys Pro Lys Thr Asp
 20 25 30

<210> 988
 <211> 125
 <212> PRT
 <213> Homo sapiens

<400> 988
 Met Ala Asp Ile Gln Thr Glu Arg Ala Tyr Gln Lys Gln Pro Thr Ile
 1 5 10 15

Phe Gln Asn Lys Lys Arg Val Leu Leu Gly Glu Thr Gly Lys Glu Lys
 20 25 30

Leu Pro Arg Val Thr Asn Lys Asn Ile Gly Leu Gly Phe Lys Asp Thr
 35 40 45

Pro Arg Arg Leu Leu Arg Gly Thr Tyr Ile Asp Lys Lys Cys Pro Phe
 50 55 60

499

Thr Gly Asn Val Ser Ile Arg Gly Arg Ile Leu Ser Gly Val Val Thr
65 70 75 80

Gln Asp Glu Asp Ala Glu Asp His Cys His Pro Pro Arg Leu Ser Ala
85 90 95

Leu His Pro Gln Val Gln Pro Leu Arg Glu Ala Pro Gln Glu His Val
100 105 110

Cys Thr Pro Val Pro Leu Leu Gln Gly Arg Pro Asp Arg
115 120 125

<210> 989

<211> 79

<212> PRT

<213> Homo sapiens

<400> 989

Met Lys Met Gln Arg Thr Ile Val Ile Arg Arg Asp Tyr Leu His Tyr
1 5 10 15

Ile Arg Lys Tyr Asn Arg Phe Glu Lys Arg His Lys Asn Met Ser Val
20 25 30

His Leu Ser Pro Cys Phe Arg Asp Val Gln Ile Gly Asp Ile Val Thr
35 40 45

Val Gly Glu Cys Arg Pro Leu Ser Lys Thr Val Arg Phe Asn Val Leu
50 55 60

Lys Val Thr Lys Ala Ala Gly Thr Lys Lys Gln Phe Gln Lys Phe
65 70 75

<210> 990

<211> 30

<212> PRT

<213> Homo sapiens

<400> 990

Met Ala Asp Ile Gln Thr Glu Arg Ala Tyr Gln Lys Gln Pro Thr Ile
1 5 10 15

Phe Gln Asn Lys Lys Arg Val Leu Leu Gly Glu Thr Gly Lys
20 25 30

<210> 991

<211> 58

<212> PRT

<213> Homo sapiens

<400> 991

Lys Leu Pro Arg Val Thr Asn Lys Asn Ile Gly Leu Gly Phe Lys Asp
1 5 10 15

Thr Pro Arg Arg Leu Leu Arg Gly Thr Tyr Ile Asp Lys Lys Cys Pro
20 25 30

Phe Thr Gly Asn Val Ser Ile Arg Gly Arg Ile Leu Ser Gly Val Val
35 40 45

Thr Gln Asp Glu Asp Ala Glu Asp His Cys
50 55

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<210> 992
<211> 38
<212> PRT
<213> Homo sapiens
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<400> 992
His Cys His Pro Pro Arg Leu Ser Ala Leu His Pro Gln Val Gln Pro
1 5 10 15

Leu Arg Glu Ala Pro Gln Glu His Val Cys Thr Pro Val Pro Leu Leu
20 25 30

Gln Gly Arg Pro Asp Arg
35

```
<210> 993
<211> 36
<212> PRT
<213> Homo sapiens
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<400> 993
Met Lys Met Gln Arg Thr Ile Val Ile Arg Arg Asp Tyr Leu His Tyr
1 5 10 15

Ile Arg Lys Tyr Asn Arg Phe Glu Lys Arg His Lys Asn Met Ser Val
20 25 30

His Leu Ser Pro
35

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<210> 994
<211> 43
<212> PRT
<213> Homo sapiens
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<400> 994
Cys Phe Arg Asp Val Gln Ile Gly Asp Ile Val Thr Val Gly Glu Cys
1 5 10 15

Arg Pro Leu Ser Lys Thr Val Arg Phe Asn Val Leu Lys Val Thr Lys
20 25 30

Ala Ala Gly Thr Lys Lys Gln Phe Gln Lys Phe
35 40

501

<210> 995
 <211> 33
 <212> PRT
 <213> Homo sapiens

<400> 995
 Pro Arg Arg Leu Leu Arg Gly Thr Tyr Ile Asp Lys Lys Cys Pro Phe
 1 5 10 15

Thr Gly Asn Val Ser Ile Arg Gly Arg Ile Leu Ser Gly Val Val Thr
 20 25 30

Gln

<210> 996
 <211> 29
 <212> PRT
 <213> Homo sapiens

<400> 996
 Ser Arg Gly Thr Gly Val Gln Thr Cys Ser Cys Gly Ala Ser Arg Ser
 1 5 10 15

Gly Cys Thr Cys Gly Cys Ser Ala Asp Ser Leu Gly Gly
 20 25

<210> 997
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 997
 Gln Trp Ser Ser Ala Ser Ser Ser Trp Val Thr Thr Pro Glu Arg Ile
 1 5 10 15

Arg Pro Arg Met Asp Thr Leu Pro Val Lys Gly His Phe Leu Ser Met
 20 25 30

<210> 998
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 998
 Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met
 1 5 10 15

Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg
 20 25 30

Leu Ile Cys Lys Gly Thr Ile Glu Glu Arg Ile Leu Gln Arg Ala Lys

502

35 40 45
 Glu Lys Ser Glu Ile Gln Arg Met Val Ile Ser Gly
 50 55 60

<210> 999
 <211> 67
 <212> PRT
 <213> Homo sapiens.

<220>
 <221> SITE
 <222> (19)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (62)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 999
 Thr Arg Met Ile Asp Leu Leu Glu Glu Tyr Met Val Tyr Arg Lys His
 1 5 10 15

Thr Tyr Xaa Arg Leu Asp Gly Ser Ser Lys Ile Ser Glu Arg Arg Asp
 20 25 30

Met Val Ala Asp Phe Gln Asn Arg Asn Asp Ile Phe Val Phe Leu Leu
 35 40 45

Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Thr Ala Xaa Asp Thr
 50 55 60

Val His Phe
 65

<210> 1000
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 1000
 Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met
 1 5 10 15

Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg
 20 25 30

<210> 1001
 <211> 31
 <212> PRT
 <213> Homo sapiens

503

<400> 1001

Val Tyr Arg Leu Ile Cys Lys Gly Thr Ile Glu Glu Arg Ile Leu Gln
 1 5 10 15

Arg Ala Lys Glu Lys Ser Glu Ile Gln Arg Met Val Ile Ser Gly
 20 25 30

<210> 1002

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1002

Thr Arg Met Ile Asp Leu Leu Glu Glu Tyr Met Val Tyr Arg Lys His
 1 5 10 15

Thr Tyr Xaa Arg Leu Asp Gly Ser Ser Lys Ile Ser Glu Arg Arg Asp
 20 25 30

Met

<210> 1003

<211> 38

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1003

Arg Arg Asp Met Val Ala Asp Phe Gln Asn Arg Asn Asp Ile Phe Val
 1 5 10 15

Phe Leu Leu Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Thr Ala
 20 25 30

Xaa Asp Thr Val His Phe
 35

<210> 1004

<211> 37

<212> PRT

<213> Homo sapiens

<400> 1004

Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met

504

1	5	10	15
Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg			
	20	25	30

Leu Ile Cys Lys Gly
35

<210> 1005
<211> 37
<212> PRT
<213> Homo sapiens

<400> 1005
Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met
1 5 10 15

Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg
20 25 30

Leu Ile Cys Lys Gly
35

<210> 1006
<211> 29
<212> PRT
<213> Homo sapiens

<400> 1006
Arg Leu Ile Cys Lys Gly Thr Ile Glu Glu Arg Ile Leu Gln Arg Ala
1 5 10 15

Lys Glu Lys Ser Glu Ile Gln Arg Met Val Ile Ser Gly
20 25

<210> 1007
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (20)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (63)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1007
Gly Thr Arg Met Ile Asp Leu Leu Glu Glu Tyr Met Val Tyr Arg Lys
1 5 10 15

His Thr Tyr Xaa Arg Leu Asp Gly Ser Ser Lys Ile Ser Glu Arg Arg

505

	20		25		30
Asp Met Val Ala Asp Phe Gln Asn Arg Asn Asp Ile Phe Val Phe Leu					
	35		40		45
Leu Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Thr Ala Xaa Asp					
	50		55		60
Thr Val His Phe Leu					
	65				

<210> 1008

<211> 364

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (259)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (312)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1008

Met Ser Leu His Gly Lys Arg Lys Glu Ile Tyr Lys Tyr Glu Ala Pro
1 5 10 15

Trp Thr Val Tyr Ala Met Asn Trp Ser Val Arg Pro Asp Lys Arg Phe
20 25 30

Arg Leu Ala Leu Gly Ser Phe Val Glu Glu Tyr Asn Asn Lys Val Gln
35 40 45

Leu Val Gly Leu Asp Glu Glu Ser Ser Glu Phe Ile Cys Arg Asn Thr
50 55 60

Phe Asp His Pro Tyr Pro Thr Thr Lys Leu Met Trp Ile Pro Asp Thr
65 70 75 80

Lys Gly Val Tyr Pro Asp Leu Leu Ala Thr Ser Gly Asp Tyr Leu Arg
85 90 95

Val Trp Arg Val Gly Glu Thr Glu Thr Arg Leu Glu Cys Leu Leu Asn
100 105 110

Asn Asn Lys Asn Ser Asp Phe Cys Ala Pro Leu Thr Ser Phe Asp Trp
115 120 125

Asn Glu Val Asp Pro Tyr Leu Leu Gly Thr Ser Ser Ile Asp Thr Thr
130 135 140

Cys Thr Ile Trp Gly Leu Glu Thr Gly Gln Val Leu Gly Arg Val Asn
145 150 155 160

Leu	Val	Ser	Gly	His	Val	Lys	Thr	Gln	Leu	Ile	Ala	His	Asp	Lys	Glu
				165					170					175	
Val	Tyr	Asp	Ile	Ala	Phe	Ser	Arg	Ala	Gly	Gly	Gly	Arg	Asp	Met	Phe
			180					185					190		
Ala	Ser	Val	Gly	Ala	Asp	Gly	Ser	Val	Arg	Met	Phe	Asp	Leu	Arg	His
		195					200					205			
Leu	Glu	His	Ser	Thr	Ile	Ile	Tyr	Glu	Asp	Pro	Gln	His	His	Pro	Leu
	210					215					220				
Leu	Arg	Leu	Cys	Trp	Asn	Lys	Gln	Asp	Pro	Asn	Tyr	Leu	Ala	Thr	Met
225					230					235					240
Ala	Met	Asp	Gly	Met	Glu	Val	Val	Ile	Leu	Asp	Val	Arg	Val	Pro	Ala
				245					250					255	
His	Leu	Xaa	Pro	Gly	Thr	Thr	Ile	Glu	His	Val	Ser	Met	Ala	Leu	Leu
			260					265					270		
Gly	Pro	His	Ile	His	Pro	Ala	Thr	Ser	Ala	Leu	Gln	Arg	Met	Thr	Thr
		275					280					285			
Arg	Leu	Ser	Ser	Gly	Thr	Ser	Ser	Lys	Cys	Pro	Glu	Pro	Leu	Arg	Thr
	290					295					300				
Leu	Ser	Trp	Pro	Thr	Gln	Leu	Xaa	Gly	Glu	Ile	Asn	Asn	Val	Gln	Trp
305					310					315					320
Ala	Ser	Thr	Gln	Pro	Glu	Leu	Ser	Pro	Ser	Ala	Thr	Thr	Thr	Ala	Trp
				325					330					335	
Arg	Tyr	Ser	Glu	Cys	Ser	Val	Gly	Gly	Ala	Val	Pro	Thr	Arg	Gln	Gly
			340					345					350		
Leu	Leu	Tyr	Phe	Leu	Pro	Leu	Pro	His	Pro	Gln	Ser				
	355						360								

<400> 1009
Met Ser Leu His Gly Lys Arg Lys Glu Ile Tyr Lys Tyr Glu Ala Pro
1 5 10 15
Trp Thr Val Tyr Ala Met Asn Trp Ser Val Arg Pro Asp Lys Arg Phe
20 25 30
Arg Leu Ala Leu Gly Ser Phe Val Glu Glu Tyr Asn Asn Lys Val Gln
35 40 45
Leu Val Gly Leu Asp Glu Glu Ser Ser Glu Phe Ile Cys Arg Asn Thr
50 55 60

507

Phe Asp His Pro Tyr Pro Thr Thr Lys Leu Met Trp Ile Pro Asp Thr
 65 70 75 80

Lys Gly Val Tyr Pro Asp Leu Leu Ala Thr Ser Gly Asp Tyr Leu Arg
 85 90 95

Val Trp Arg Val Gly Glu Thr Glu Thr Arg Leu Glu Cys Leu Leu Asn
 100 105 110

Asn Asn Lys Asn Ser Asp Phe Cys Ala Pro Leu Thr Ser Phe Asp Trp
 115 120 125

Asn Glu Val Asp Pro Tyr Leu Leu
 130 135

<210> 1010

<211> 140

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1010

Ser Phe Asp Trp Asn Glu Val Asp Pro Tyr Leu Leu Gly Thr Ser Ser
 1 5 10 15

Ile Asp Thr Thr Cys Thr Ile Trp Gly Leu Glu Thr Gly Gln Val Leu
 20 25 30

Gly Arg Val Asn Leu Val Ser Gly His Val Lys Thr Gln Leu Ile Ala
 35 40 45

His Asp Lys Glu Val Tyr Asp Ile Ala Phe Ser Arg Ala Gly Gly Gly
 50 55 60

Arg Asp Met Phe Ala Ser Val Gly Ala Asp Gly Ser Val Arg Met Phe
 65 70 75 80

Asp Leu Arg His Leu Glu His Ser Thr Ile Ile Tyr Glu Asp Pro Gln
 85 90 95

His His Pro Leu Leu Arg Leu Cys Trp Asn Lys Gln Asp Pro Asn Tyr
 100 105 110

Leu Ala Thr Met Ala Met Asp Gly Met Glu Val Val Ile Leu Asp Val
 115 120 125

Arg Val Pro Ala His Leu Xaa Pro Gly Thr Thr Ile
 130 135 140

<210> 1011

<211> 170

<212> PRT

508

<213> Homo sapiens

<220>

<221> SITE

<222> (65)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (118)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1011

Val	Gly	Ala	Asp	Gly	Ser	Val	Arg	Met	Phe	Asp	Leu	Arg	His	Leu	Glu
1				5					10					15	

His	Ser	Thr	Ile	Ile	Tyr	Glu	Asp	Pro	Gln	His	His	Pro	Leu	Leu	Arg
			20					25					30		

Leu	Cys	Trp	Asn	Lys	Gln	Asp	Pro	Asn	Tyr	Leu	Ala	Thr	Met	Ala	Met
			35				40					45			

Asp	Gly	Met	Glu	Val	Val	Ile	Leu	Asp	Val	Arg	Val	Pro	Ala	His	Leu
	50					55					60				

Xaa	Pro	Gly	Thr	Thr	Ile	Glu	His	Val	Ser	Met	Ala	Leu	Leu	Gly	Pro
65					70					75				80	

His	Ile	His	Pro	Ala	Thr	Ser	Ala	Leu	Gln	Arg	Met	Thr	Thr	Arg	Leu
				85					90					95	

Ser	Ser	Gly	Thr	Ser	Ser	Lys	Cys	Pro	Glu	Pro	Leu	Arg	Thr	Leu	Ser
			100					105					110		

Trp	Pro	Thr	Gln	Leu	Xaa	Gly	Glu	Ile	Asn	Asn	Val	Gln	Trp	Ala	Ser
		115					120					125			

Thr	Gln	Pro	Glu	Leu	Ser	Pro	Ser	Ala	Thr	Thr	Thr	Ala	Trp	Arg	Tyr
	130					135						140			

Ser	Glu	Cys	Ser	Val	Gly	Gly	Ala	Val	Pro	Thr	Arg	Gln	Gly	Leu	Leu
145					150					155				160	

Tyr	Phe	Leu	Pro	Leu	Pro	His	Pro	Gln	Ser
			165					170	

<210> 1012

<211> 286

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

509

<221> SITE

<222> (258)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1012

Leu	Tyr	Ala	Thr	Ala	Thr	Val	Ile	Ser	Ser	Pro	Ser	Thr	Glu	Xaa	Leu	1	5	10	15
Ser	Gln	Asp	Gln	Gly	Asp	Arg	Ala	Ser	Leu	Asp	Ala	Ala	Asp	Ser	Gly	20	25	30	
Arg	Gly	Ser	Trp	Thr	Ser	Cys	Ser	Ser	Gly	Ser	His	Asp	Asn	Ile	Gln	35	40	45	
Thr	Ile	Gln	His	Gln	Arg	Ser	Trp	Glu	Thr	Leu	Pro	Phe	Gly	His	Thr	50	55	60	
His	Phe	Asp	Tyr	Ser	Gly	Asp	Pro	Ala	Gly	Leu	Trp	Ala	Ser	Ser	Ser	65	70	75	80
His	Met	Asp	Gln	Ile	Met	Phe	Ser	Asp	His	Ser	Thr	Lys	Tyr	Asn	Arg	85	90	95	
Gln	Asn	Gln	Ser	Arg	Glu	Ser	Leu	Glu	Gln	Ala	Gln	Ser	Arg	Ala	Ser	100	105	110	
Trp	Ala	Ser	Ser	Thr	Gly	Tyr	Trp	Gly	Glu	Asp	Ser	Glu	Gly	Asp	Thr	115	120	125	
Gly	Thr	Ile	Lys	Arg	Arg	Gly	Gly	Lys	Asp	Val	Ser	Ile	Glu	Ala	Glu	130	135	140	
Ser	Ser	Ser	Leu	Thr	Ser	Val	Thr	Thr	Glu	Glu	Thr	Lys	Pro	Val	Pro	145	150	155	160
Met	Pro	Ala	His	Ile	Ala	Val	Ala	Ser	Ser	Thr	Thr	Lys	Gly	Leu	Ile	165	170	175	
Ala	Arg	Lys	Glu	Gly	Arg	Tyr	Arg	Glu	Pro	Pro	Pro	Thr	Pro	Pro	Gly	180	185	190	
Tyr	Ile	Gly	Ile	Pro	Ile	Thr	Asp	Phe	Pro	Glu	Gly	His	Ser	His	Pro	195	200	205	
Ala	Arg	Lys	Pro	Pro	Asp	Tyr	Asn	Val	Ala	Leu	Gln	Arg	Ser	Arg	Met	210	215	220	
Val	Ala	Arg	Ser	Ser	Asp	Thr	Ala	Gly	Pro	Ser	Ser	Val	Gln	Gln	Pro	225	230	235	240
His	Gly	His	Pro	Thr	Ser	Ser	Arg	Pro	Val	Asn	Lys	Pro	Gln	Trp	His	245	250	255	
Lys	Xaa	Asn	Glu	Ser	Asp	Pro	Arg	Leu	Ala	Pro	Tyr	Gln	Ser	Gln	Gly	260	265	270	
Phe	Ser	Thr	Glu	Glu	Asp	Glu	Asp	Glu	Gln	Val	Ser	Ala	Val			275	280	285	

510

<210> 1013

<211> 42

<212> PRT

<213> Homo sapiens

<400> 1013

His Met Asp Gln Ile Met Phe Ser Asp His Ser Thr Lys Tyr Asn Arg
1 5 10 15

Gln Asn Gln Ser Arg Glu Ser Leu Glu Gln Ala Gln Ser Arg Ala Ser
20 25 30

Trp Ala Ser Ser Thr Gly Tyr Trp Gly Glu
35 40

<210> 1014

<211> 51

<212> PRT

<213> Homo sapiens

<400> 1014

Ser Val Thr Thr Glu Glu Thr Lys Pro Val Pro Met Pro Ala His Ile
1 5 10 15

Ala Val Ala Ser Ser Thr Thr Lys Gly Leu Ile Ala Arg Lys Glu Gly
20 25 30

Arg Tyr Arg Glu Pro Pro Pro Thr Pro Pro Gly Tyr Ile Gly Ile Pro
35 40 45

Ile Thr Asp
50

<210> 1015

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1015

Val Ala Leu Gln Arg Ser Arg Met Val Ala Arg Ser Ser Asp Thr Ala
1 5 10 15

Gly Pro Ser Ser Val Gln Gln Pro His Gly His Pro Thr Ser Ser Arg
20 25 30

Pro Val Asn Lys Pro Gln Trp His Lys Xaa Asn Glu Ser Asp Pro Arg
35 40 45

Leu Ala Pro Tyr Gln Ser Gln Gly Phe

511

50

55

<210> 1016

<211> 41

<212> PRT

<213> Homo sapiens

<400> 1016

Cys Leu Leu Phe Val Phe Val Ser Leu Gly Met Arg Cys Leu Phe Trp
 1 5 10 15

Thr Ile Val Tyr Asn Val Leu Tyr Leu Lys His Lys Cys Asn Thr Val
 20 25 30

Leu Leu Cys Tyr His Leu Cys Ser Ile
 35 40

<210> 1017

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (46)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (65)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1017

Ala Cys Ser Lys Leu Ile Pro Ala Phe Glu Met Val Met Arg Ala Lys
 1 5 10 15

Asp Asn Val Tyr His Leu Asp Cys Phe Ala Cys Gln Leu Cys Asn Gln
 20 25 30

Arg Xaa Cys Val Gly Asp Lys Phe Phe Leu Lys Asn Asn Xaa Xaa Leu
 35 40 45

Cys Gln Thr Asp Tyr Glu Glu Gly Leu Met Lys Glu Gly Tyr Ala Pro
 50 55 60

Xaa Val Arg

512

65

<210> 1018

<211> 45

<212> PRT

<213> Homo sapiens

<400> 1018

Ser Ala Leu Ser Glu Pro Gly Ala Pro Asp Arg Arg Arg Pro Cys Pro
 1 5 10 15

Glu Ser Val Pro Arg Arg Pro Asp Asp Glu Gln Trp Pro Pro Pro Thr
 20 25 30

Ala Leu Cys Leu Asp Val Ala Pro Leu Pro Pro Ser Ser
 35 40 45

<210> 1019

<211> 43

<212> PRT

<213> Homo sapiens

<400> 1019

Pro Val Gly Tyr Leu Asp Lys Gln Val Pro Asp Thr Ser Val Gln Glu
 1 5 10 15

Thr Asp Arg Ile Leu Val Glu Lys Arg Cys Trp Asp Ile Ala Leu Gly
 20 25 30

Pro Leu Lys Gln Ile Pro Met Asn Leu Phe Ile
 35 40

<210> 1020

<211> 214

<212> PRT

<213> Homo sapiens

<400> 1020

Ala His Ala Ser Glu Ser Gly Glu Arg Trp Trp Ala Cys Cys Gly Val
 1 5 10 15

Arg Phe Gly Leu Arg Ser Ile Glu Ala Ile Gly Arg Ser Cys Cys His
 20 25 30

Asp Gly Pro Gly Gly Leu Val Ala Asn Arg Gly Arg Arg Phe Lys Trp
 35 40 45

Ala Ile Glu Leu Ser Gly Pro Gly Gly Gly Ser Arg Gly Arg Ser Asp
 50 55 60

Arg Gly Ser Gly Gln Gly Asp Ser Leu Tyr Pro Val Gly Tyr Leu Asp
 65 70 75 80

Lys Gln Val Pro Asp Thr Ser Val Gln Glu Thr Asp Arg Ile Leu Val
 85 90 95

513

Glu Lys Arg Cys Trp Asp Ile Ala Leu Gly Pro Leu Lys Gln Ile Pro
 100 105 110
 Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe
 115 120 125
 Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu
 130 135 140
 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys
 145 150 155 160
 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala
 165 170 175
 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala
 180 185 190
 Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Phe Ser
 195 200 205
 Gly Gly Gly Leu Leu Leu
 210

<210> 1021
 <211> 46
 <212> PRT
 <213> Homo sapiens

<400> 1021
 Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys Phe Leu Gln Gly
 1 5 10 15
 Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala Leu Ala Val Tyr
 20 25 30
 Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala Ser Asp
 35 40 45

<210> 1022
 <211> 43
 <212> PRT
 <213> Homo sapiens

<400> 1022
 Pro Val Gly Tyr Leu Asp Lys Gln Val Pro Asp Thr Ser Val Gln Glu
 1 5 10 15
 Thr Asp Arg Ile Leu Val Glu Lys Arg Cys Trp Asp Ile Ala Leu Gly
 20 25 30
 Pro Leu Lys Gln Ile Pro Met Asn Leu Phe Ile
 35 40

514

<210> 1023

<211> 48

<212> PRT

<213> Homo sapiens

<400> 1023

Pro Thr Thr Lys Leu Asp Ile Met Glu Lys Lys Lys His Ile Gln Ile
 1 5 10 15

Arg Phe Pro Ser Phe Tyr His Lys Leu Val Asp Ser Gly Arg Met Arg
 20 25 30

Ser Lys Arg Glu Thr Arg Arg Glu Asp Ser Asp Thr Lys His Asn Leu
 35 40 45

<210> 1024

<211> 16

<212> PRT

<213> Homo sapiens

<400> 1024

Phe Leu Trp Lys Ser Leu Leu Leu Arg Tyr Phe Lys Met Arg Gln His
 1 5 10 15

<210> 1025

<211> 36

<212> PRT

<213> Homo sapiens

<400> 1025

Tyr His Tyr Leu Leu Ser Ser Phe Leu Ser Tyr Ser Ser Ser Ser Gln
 1 5 10 15

Asn Leu Pro Val Tyr Gly Arg Lys Met Gly Thr Leu Phe Glu Cys Val
 20 25 30

Phe Phe Phe Pro
 35

<210> 1026

<211> 167

<212> PRT

<213> Homo sapiens

<400> 1026

Thr Glu His Ile Ile Ala Val Met Ile Thr Glu Leu Arg Gly Lys Asp
 1 5 10 15

Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val Gln Met Thr Ile Ala

515

	20		25		30	
Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser Arg Gly Ser Leu Val	35		40		45	
Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile Ile Ser Ser Ala Trp	50		55		60	
Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr Thr Asn Ala Arg Asp	65		70		75	80
Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys Lys Ala Ile Ser Lys		85		90		95
Leu Thr Thr Arg Thr Val Lys Lys Gly Asp Lys Glu Thr Asp Pro Asp		100		105		110
Phe Asp His Cys Ala Val Cys Ile Glu Ser Tyr Lys Gln Asn Asp Val		115		120		125
Val Arg Ile Leu Pro Cys Lys His Val Phe His Lys Ser Cys Val Asp		130		135		140
Pro Trp Leu Ser Glu His Cys Thr Cys Pro Met Cys Lys Leu Asn Ile		145		150		155
						160
Leu Lys Ala Leu Gly Ile Val						165

<210> 1027

<211> 276

<212> PRT

<213> Homo sapiens

<400> 1027

Met Thr His Pro Gly Thr Glu His Ile Ile Ala Val Met Ile Thr Glu	1		5		10		15
Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val		20		25		30	
Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser		35		40		45	
Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile		50		55		60	
Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr		65		70		75	80
Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys			85		90		95
Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys Gly Asp Lys		100		105		110	
Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile Glu Ser Tyr							

516

115	120	125
Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His Val Phe His 130 135 140		
Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr Cys Pro Met 145 150 155 160		
Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro Asn Leu Pro 165 170 175		
Cys Thr Asp Asn Val Ala Phe Asp Met Glu Arg Leu Thr Arg Thr Gln 180 185 190		
Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp Asn Ser 195 200 205		
Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu Pro Gln 210 215 220		
Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala Val Thr 225 230 235 240		
Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala Leu Thr 245 250 255		
Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala Asn Glu 260 265 270		
Val Glu Trp Phe 275		

<210> 1028
 <211> 69
 <212> PRT
 <213> Homo sapiens

<400> 1028
 Thr Glu His Ile Ile Ala Val Met Ile Thr Glu Leu Arg Gly Lys Asp
 1 5 10 15
 Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val Gln Met Thr Ile Ala
 20 25 30
 Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser Arg Gly Ser Leu Val
 35 40 45
 Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile Ile Ser Ser Ala Trp
 50 55 60
 Leu Ile Phe Tyr Phe
 65

<210> 1029
 <211> 58
 <212> PRT

517

<213> Homo sapiens

<400> 1029

Ser Ile Ser Phe Ile Val Leu Met Ile Ile Ser Ser Ala Trp Leu Ile
 1 5 10 15

Phe Tyr Phe Ile Gln Lys Ile Arg Tyr Thr Asn Ala Arg Asp Arg Asn
 20 25 30

Gln Arg Arg Leu Gly Asp Ala Ala Lys Lys Ala Ile Ser Lys Leu Thr
 35 40 45

Thr Arg Thr Val Lys Lys Gly Asp Lys Glu
 50 55

<210> 1030

<211> 66

<212> PRT

<213> Homo sapiens

<400> 1030

Val Lys Lys Gly Asp Lys Glu Thr Asp Pro Asp Phe Asp His Cys Ala
 1 5 10 15

Val Cys Ile Glu Ser Tyr Lys Gln Asn Asp Val Val Arg Ile Leu Pro
 20 25 30

Cys Lys His Val Phe His Lys Ser Cys Val Asp Pro Trp Leu Ser Glu
 35 40 45

His Cys Thr Cys Pro Met Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly
 50 55 60

Ile Val
 65

<210> 1031

<211> 106

<212> PRT

<213> Homo sapiens

<400> 1031

Met Thr His Pro Gly Thr Glu His Ile Ile Ala Val Met Ile Thr Glu
 1 5 10 15

Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val
 20 25 30

Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser
 35 40 45

Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile
 50 55 60

Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr
 65 70 75 80

Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys
85 90 95

Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr
100 105

<213> Homo sapiens

Ala Ala Lys Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys
1 5 10 15

Gly Asp Lys Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile
20 25 30

Glu Ser Tyr Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His
35 40 45

Val Phe His Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr
50 55 60

Cys Pro Met Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro
65 70 75 80

Asn Leu Pro Cys

<213> Homo sapiens

Thr Gln Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp
1 5 10 15

Asn Ser Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu
20 25 30

Pro Gln Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala
35 40 45

Val Thr Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala
50 55 60

Leu Thr Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala
65 70 75 80

Asn Glu Val Glu Trp Phe
85

519

<210> 1034

<211> 341

<212> PRT

<213> Homo sapiens

<400> 1034

Pro Leu His Gly Val Ala Asp His Leu Gly Cys Asp Pro Gln Thr Arg
 1 5 10 15
 Phe Phe Val Pro Pro Asn Ile Lys Gln Trp Ile Ala Leu Leu Gln Arg
 20 25 30
 Gly Asn Cys Thr Phe Lys Glu Lys Ile Ser Arg Ala Ala Phe His Asn
 35 40 45
 Ala Val Ala Val Val Ile Tyr Asn Asn Lys Ser Lys Glu Glu Pro Val
 50 55 60
 Thr Met Thr His Pro Gly Thr Glu His Ile Ile Ala Val Met Ile Thr
 65 70 75 80
 Glu Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser
 85 90 95
 Val Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe
 100 105 110
 Ser Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met
 115 120 125
 Ile Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg
 130 135 140
 Tyr Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala
 145 150 155 160
 Lys Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys Gly Asp
 165 170 175
 Lys Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile Glu Ser
 180 185 190
 Tyr Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His Val Phe
 195 200 205
 His Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr Cys Pro
 210 215 220
 Met Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro Asn Leu
 225 230 235 240
 Pro Cys Thr Asp Asn Val Ala Phe Asp Met Glu Arg Leu Thr Arg Thr
 245 250 255
 Gln Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp Asn
 260 265 270
 Ser Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu Pro

520

275 280 285
 Gln Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala Val
 290 295 300
 Thr Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala Leu
 305 310 315 320
 Thr Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala Asn
 325 330 335
 Glu Val Glu Trp Phe
 340

<210> 1035
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 1035
 His Gly Val Ala Asp His Leu Gly Cys Asp Pro Gln Thr Arg Phe Phe
 1 5 10 15
 Val Pro Pro Asn Ile Lys Gln Trp Ile Ala Leu Leu Gln Arg Gly Asn
 20 25 30
 Cys Thr Phe Lys Glu Lys Ile Ser Arg Ala Ala Phe His Asn Ala Val
 35 40 45
 Ala Val Val Ile Tyr Asn Asn Lys Ser Lys Glu Glu
 50 55 60

<210> 1036
 <211> 314
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (189)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1036
 Met Ser Gly Gln Gly Leu Ala Gly Phe Phe Ala Ser Val Ala Met Ile
 1 5 10 15
 Cys Ala Ile Ala Ser Gly Ser Glu Leu Ser Glu Ser Ala Phe Gly Tyr
 20 25 30
 Phe Ile Thr Ala Cys Ala Val Ile Ile Leu Thr Ile Ile Cys Tyr Leu
 35 40 45
 Gly Leu Pro Arg Leu Glu Phe Tyr Arg Tyr Tyr Gln Gln Leu Lys Leu
 50 55 60
 Glu Gly Pro Gly Glu Gln Glu Thr Lys Leu Asp Leu Ile Ser Lys Gly

65				70				75				80			
Glu	Glu	Pro	Arg	Ala	Gly	Lys	Glu	Glu	Ser	Gly	Val	Ser	Val	Ser	Asn
				85					90						95
Ser	Gln	Pro	Thr	Asn	Glu	Ser	His	Ser	Ile	Lys	Ala	Ile	Leu	Lys	Asn
			100					105					110		
Ile	Ser	Val	Leu	Ala	Phe	Ser	Val	Cys	Phe	Ile	Phe	Thr	Ile	Thr	Ile
		115					120					125			
Gly	Met	Phe	Pro	Ala	Val	Thr	Val	Glu	Val	Lys	Ser	Ser	Ile	Ala	Gly
	130					135					140				
Ser	Ser	Thr	Trp	Glu	Arg	Tyr	Phe	Ile	Pro	Val	Ser	Cys	Phe	Leu	Thr
145					150					155					160
Phe	Asn	Ile	Phe	Asp	Trp	Leu	Gly	Arg	Ser	Leu	Thr	Ala	Val	Phe	Met
				165					170					175	
Trp	Pro	Gly	Lys	Asp	Ser	Arg	Trp	Leu	Pro	Ser	Trp	Xaa	Leu	Ala	Arg
			180					185					190		
Leu	Val	Phe	Val	Pro	Leu	Leu	Leu	Leu	Cys	Asn	Ile	Lys	Pro	Arg	Arg
		195					200					205			
Tyr	Leu	Thr	Val	Val	Phe	Glu	His	Asp	Ala	Trp	Phe	Ile	Phe	Phe	Met
	210					215					220				
Ala	Ala	Phe	Ala	Phe	Ser	Asn	Gly	Tyr	Leu	Ala	Ser	Leu	Cys	Met	Cys
225					230					235					240
Phe	Gly	Pro	Lys	Lys	Val	Lys	Pro	Ala	Glu	Ala	Glu	Thr	Ala	Glu	Pro
				245					250					255	
Ser	Trp	Pro	Ser	Ser	Cys	Val	Trp	Val	Trp	His	Trp	Gly	Leu	Phe	Ser
			260					265					270		
Pro	Ser	Cys	Ser	Gly	Gln	Leu	Cys	Asp	Lys	Gly	Trp	Thr	Glu	Gly	Leu
		275					280					285			
Pro	Ala	Ser	Leu	Pro	Val	Cys	Leu	Leu	Pro	Leu	Pro	Ser	Ala	Arg	Gly
	290					295					300				
Asp	Pro	Glu	Trp	Ser	Gly	Gly	Phe	Phe	Phe						
305					310										

Cys Ala Ile Ala Ser Gly Ser Glu Leu Ser Glu Ser Ala Phe Gly Tyr

522

20 25 30
 Phe Ile Thr Ala Cys Ala Val Ile Ile Leu Thr Ile Ile Cys Tyr Leu
 35 40 45
 Gly Leu Pro Arg Leu Glu Phe Tyr Arg Tyr Tyr Gln Gln Leu Lys Leu
 50 55 60
 Glu Gly Pro Gly Glu Gln Glu Thr Lys Leu Asp Leu Ile Ser Lys Gly
 65 70 75 80
 Glu Glu Pro Arg Ala Gly Lys Glu Glu Ser Gly Val Ser Val Ser Asn
 85 90 95
 Ser Gln Pro Thr Asn Glu Ser His Ser Ile
 100 105

<210> 1038
 <211> 81
 <212> PRT
 <213> Homo sapiens

<400> 1038
 Ser Gly Val Ser Val Ser Asn Ser Gln Pro Thr Asn Glu Ser His Ser
 1 5 10 15
 Ile Lys Ala Ile Leu Lys Asn Ile Ser Val Leu Ala Phe Ser Val Cys
 20 25 30
 Phe Ile Phe Thr Ile Thr Ile Gly Met Phe Pro Ala Val Thr Val Glu
 35 40 45
 Val Lys Ser Ser Ile Ala Gly Ser Ser Thr Trp Glu Arg Tyr Phe Ile
 50 55 60
 Pro Val Ser Cys Phe Leu Thr Phe Asn Ile Phe Asp Trp Leu Gly Arg
 65 70 75 80
 Ser

<210> 1039
 <211> 92
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (63)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1039
 Thr Ile Gly Met Phe Pro Ala Val Thr Val Glu Val Lys Ser Ser Ile
 1 5 10 15
 Ala Gly Ser Ser Thr Trp Glu Arg Tyr Phe Ile Pro Val Ser Cys Phe

523

	20		25		30	
Leu Thr Phe Asn Ile Phe Asp Trp Leu Gly Arg Ser Leu Thr Ala Val						
	35		40		45	
Phe Met Trp Pro Gly Lys Asp Ser Arg Trp Leu Pro Ser Trp Xaa Leu						
	50		55		60	
Ala Arg Leu Val Phe Val Pro Leu Leu Leu Cys Asn Ile Lys Pro						
	65		70		75	80
Arg Arg Tyr Leu Thr Val Val Phe Glu His Asp Ala						
	85		90			

<210> 1040
 <211> 74
 <212> PRT
 <213> Homo sapiens

<400> 1040
Phe Gly Pro Lys Lys Val Lys Pro Ala Glu Ala Glu Thr Ala Glu Pro
1 5 10 15
Ser Trp Pro Ser Ser Cys Val Trp Val Trp His Trp Gly Leu Phe Ser
20 25 30
Pro Ser Cys Ser Gly Gln Leu Cys Asp Lys Gly Trp Thr Glu Gly Leu
35 40 45
Pro Ala Ser Leu Pro Val Cys Leu Leu Pro Leu Pro Ser Ala Arg Gly
50 55 60
Asp Pro Glu Trp Ser Gly Gly Phe Phe Phe
65 70

<210> 1041
 <211> 135
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (96)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (97)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (98)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (99)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (101)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (102)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (103)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (104)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (105)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (106)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (107)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (108)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (109)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (110)
<223> Xaa equals any of the naturally occurring L-amino acids

525

<220>
 <221> SITE
 <222> (111)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (112)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (130)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1041
 Asp Asp Asp Gly Phe Glu Ile Val Pro Ile Glu Asp Pro Ala Lys His
 1 5 10 15
 Arg Ile Leu Asp Pro Glu Gly Leu Ala Leu Gly Ala Val Ile Ala Ser
 20 25 30
 Ser Lys Lys Ala Lys Arg Asp Leu Ile Asp Asn Ser Phe Asn Arg Tyr
 35 40 45
 Thr Phe Asn Glu Asp Glu Gly Glu Leu Pro Glu Trp Phe Val Gln Glu
 50 55 60
 Glu Lys Gln His Arg Ile Arg Gln Leu Pro Val Gly Lys Lys Glu Val
 65 70 75 80
 Glu His Tyr Arg Lys Arg Trp Arg Glu Ile Asn Ala Arg Pro Ile Xaa
 85 90 95
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110
 Leu Glu Gln Thr Arg Lys Lys Ala Glu Ala Val Val Asn Thr Val Asp
 115 120 125
 Ile Xaa Arg Thr Arg Glu Ser
 130 135

<210> 1042
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 1042
 Asp Asp Asp Gly Phe Glu Ile Val Pro Ile Glu Asp Pro Ala Lys His
 1 5 10 15
 Arg Ile Leu Asp Pro Glu Gly Leu Ala Leu Gly Ala Val Ile Ala Ser
 20 25 30
 Ser Lys Lys Ala Lys Arg Asp Leu Ile Asp Asn Ser Phe Asn Arg Tyr

526

35

40

45

Thr Phe

50

<210> 1043

<211> 51

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (13)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (16)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (20)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

527

<222> (21)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (23)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (26)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (46)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1043

Lys	Arg	Trp	Arg	Glu	Ile	Asn	Ala	Arg	Pro	Ile	Xaa	Xaa	Xaa	Xaa	Xaa
1				5					10					15	

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Leu	Glu	Gln	Thr
			20					25						30		

Arg	Lys	Lys	Ala	Glu	Ala	Val	Val	Asn	Thr	Val	Asp	Ile	Xaa	Arg	Thr
		35						40					45		

Arg	Glu	Ser
		50

<210> 1044

528

<211> 216

<212> PRT

<213> Homo sapiens

<400> 1044

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Met Ile Lys Asp Lys Gly Arg Ala Arg Thr Ala Leu Thr Ser Ser Gln
 1             5             10             15

Pro Ala His Leu Cys Pro Glu Asn Pro Leu Leu His Leu Lys Ala Ala
      20             25             30

Val Lys Glu Lys Lys Arg Asn Lys Lys Lys Lys Thr Ile Gly Ser Pro
      35             40             45

Lys Arg Ile Gln Ser Pro Leu Asn Asn Lys Leu Leu Asn Ser Pro Ala
      50             55             60

Lys Thr Leu Pro Gly Ala Cys Gly Ser Pro Gln Lys Leu Ile Asp Gly
      65             70             75             80

Phe Leu Lys His Glu Gly Pro Pro Ala Glu Lys Pro Leu Glu Glu Leu
      85             90             95

Ser Ala Ser Thr Ser Gly Val Pro Gly Leu Ser Ser Leu Gln Ser Asp
      100            105            110

Pro Ala Gly Cys Val Arg Pro Pro Ala Pro Asn Leu Ala Gly Ala Val
      115            120            125

Glu Phe Asn Asp Val Lys Thr Leu Leu Arg Glu Trp Ile Thr Thr Ile
      130            135            140

Ser Asp Pro Met Glu Glu Asp Ile Leu Gln Val Val Lys Tyr Cys Thr
      145            150            155            160

Asp Leu Ile Glu Glu Lys Asp Leu Glu Lys Leu Asp Leu Val Ile Lys
      165            170            175

Tyr Met Lys Arg Leu Met Gln Gln Ser Val Glu Ser Val Trp Asn Met
      180            185            190

Ala Phe Asp Phe Ile Leu Asp Asn Val Gln Val Val Leu Gln Gln Thr
      195            200            205

Tyr Gly Ser Thr Leu Lys Val Thr
      210            215

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<210> 1045

<211> 52

<212> PRT

<213> Homo sapiens

<400> 1045

```

Met Ile Lys Asp Lys Gly Arg Ala Arg Thr Ala Leu Thr Ser Ser Gln
 1             5             10             15

Pro Ala His Leu Cys Pro Glu Asn Pro Leu Leu His Leu Lys Ala Ala

```

529

20 25 30
 Val Lys Glu Lys Lys Arg Asn Lys Lys Lys Lys Thr Ile Gly Ser Pro
 35 40 45

Lys Arg Ile Gln
 50

<210> 1046

<211> 100

<212> PRT

<213> Homo sapiens

<400> 1046

Lys Arg Ile Gln Ser Pro Leu Asn Asn Lys Leu Leu Asn Ser Pro Ala
 1 5 10 15

Lys Thr Leu Pro Gly Ala Cys Gly Ser Pro Gln Lys Leu Ile Asp Gly
 20 25 30

Phe Leu Lys His Glu Gly Pro Pro Ala Glu Lys Pro Leu Glu Glu Leu
 35 40 45

Ser Ala Ser Thr Ser Gly Val Pro Gly Leu Ser Ser Leu Gln Ser Asp
 50 55 60

Pro Ala Gly Cys Val Arg Pro Pro Ala Pro Asn Leu Ala Gly Ala Val
 65 70 75 80

Glu Phe Asn Asp Val Lys Thr Leu Leu Arg Glu Trp Ile Thr Thr Ile
 85 90 95

Ser Asp Pro Met
 100

<210> 1047

<211> 74

<212> PRT

<213> Homo sapiens

<400> 1047

Thr Ile Ser Asp Pro Met Glu Glu Asp Ile Leu Gln Val Val Lys Tyr
 1 5 10 15

Cys Thr Asp Leu Ile Glu Glu Lys Asp Leu Glu Lys Leu Asp Leu Val
 20 25 30

Ile Lys Tyr Met Lys Arg Leu Met Gln Gln Ser Val Glu Ser Val Trp
 35 40 45

Asn Met Ala Phe Asp Phe Ile Leu Asp Asn Val Gln Val Val Leu Gln
 50 55 60

Gln Thr Tyr Gly Ser Thr Leu Lys Val Thr
 65 70

530

<210> 1048

<211> 156

<212> PRT

<213> Homo sapiens

<400> 1048

Val Cys Cys Lys Thr Thr Trp Thr Leu Ser Arg Ile Lys Ser Asn Ala
 1 5 10 15
 Ile Phe Gln Thr Asp Ser Thr Asp Cys Cys Ile Ser Leu Phe Met Tyr
 20 25 30
 Phe Ile Thr Arg Ser Ser Phe Ser Lys Ser Phe Ser Ser Ile Arg Ser
 35 40 45
 Val Gln Tyr Phe Thr Thr Trp Arg Met Ser Ser Ser Ile Gly Ser Glu
 50 55 60
 Ile Val Val Ile His Ser Leu Ser Lys Val Phe Thr Ser Leu Asn Ser
 65 70 75 80
 Thr Ala Pro Ala Arg Leu Gly Ala Gly Gly Leu Thr Gln Pro Ala Gly
 85 90 95
 Ser Asp Cys Lys Leu Glu Arg Pro Gly Thr Pro Glu Val Glu Ala Glu
 100 105 110
 Ser Ser Ser Arg Gly Phe Ser Ala Gly Gly Pro Ser Cys Phe Arg Asn
 115 120 125
 Pro Ser Ile Asn Phe Trp Gly Leu Pro Gln Ala Pro Gly Arg Val Phe
 130 135 140
 Ala Gly Leu Leu Ser Ser Leu Leu Phe Lys Gly Leu
 145 150 155

<210> 1049

<211> 25

<212> PRT

<213> Homo sapiens

<400> 1049

Trp Thr Leu Ser Arg Ile Lys Ser Asn Ala Ile Phe Gln Thr Asp Ser
 1 5 10 15
 Thr Asp Cys Cys Ile Ser Leu Phe Met
 20 25

<210> 1050

<211> 37

<212> PRT

<213> Homo sapiens

<400> 1050

Phe Thr Thr Trp Arg Met Ser Ser Ser Ile Gly Ser Glu Ile Val Val

531

1 5 10 15
Ile His Ser Leu Ser Lys Val Phe Thr Ser Leu Asn Ser Thr Ala Pro
20 25 30
Ala Arg Leu Gly Ala
35

<210> 1051
<211> 28
<212> PRT
<213> Homo sapiens

<400> 1051
Gly Gly Pro Ser Cys Phe Arg Asn Pro Ser Ile Asn Phe Trp Gly Leu
1 5 10 15
Pro Gln Ala Pro Gly Arg Val Phe Ala Gly Leu Leu
20 25

<210> 1052
<211> 18
<212> PRT
<213> Homo sapiens

<400> 1052
Phe Cys His Asp Cys Lys Phe Pro Glu Ala Ser Pro Ala Met Asn Cys
1 5 10 15

Glu Pro

<210> 1053
<211> 18
<212> PRT
<213> Homo sapiens

<400> 1053
Phe Cys His Asp Cys Lys Phe Pro Glu Ala Ser Pro Ala Met Asn Cys
1 5 10 15

Glu Pro

<210> 1054
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1054
His Glu Pro Tyr Ala Val Leu Val Ile
1 5

532

<210> 1055
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 1055
 Pro Gln Pro Ser Asn Phe Pro Thr Thr Val Arg Asn Leu Pro Tyr Ser
 1 5 10 15
 Gly Ala Gly Ala Gln Pro Pro Pro Ser Asn Cys
 20 25

<210> 1056
 <211> 134
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (130)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1056
 Met Ala Ser Ser Val Pro Ala Gly Gly His Thr Arg Ala Gly Gly Ile
 1 5 10 15
 Phe Leu Ile Gly Lys Leu Asp Leu Glu Ala Ser Leu Phe Lys Ser Phe
 20 25 30
 Gln Trp Leu Pro Phe Val Leu Arg Lys Lys Cys Asn Phe Phe Cys Trp
 35 40 45
 Asp Ser Ser Ala His Ser Leu Pro Leu His Pro Leu Ser Ala Ser Cys
 50 55 60
 Ser Ala Pro Ala Cys His Ala Ser Asp Thr His Leu Leu Tyr Pro Ser
 65 70 75 80
 Thr Arg Ala Leu Cys Pro Ser Ile Phe Ala Trp Leu Val Ala Pro His
 85 90 95
 Ser Val Phe Arg Thr Asn Ala Pro Gly Pro Thr Pro Ser Ser Gln Ser
 100 105 110
 Ser Pro Val Phe Pro Val Phe Pro Val Ser Phe Met Ala Leu Ile Val
 115 120 125
 Cys Xaa Leu Val Cys Cys
 130

<210> 1057
 <211> 71
 <212> PRT
 <213> Homo sapiens

<400> 1057

533

Met Ala Ser Ser Val Pro Ala Gly Gly His Thr Arg Ala Gly Gly Ile
 1 5 10 15
 Phe Leu Ile Gly Lys Leu Asp Leu Glu Ala Ser Leu Phe Lys Ser Phe
 20 25 30
 Gln Trp Leu Pro Phe Val Leu Arg Lys Lys Cys Asn Phe Phe Cys Trp
 35 40 45
 Asp Ser Ser Ala His Ser Leu Pro Leu His Pro Leu Ser Ala Ser Cys
 50 55 60
 Ser Ala Pro Ala Cys His Ala
 65 70

<210> 1058
 <211> 46
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (42)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1058
 Phe Ala Trp Leu Val Ala Pro His Ser Val Phe Arg Thr Asn Ala Pro
 1 5 10 15
 Gly Pro Thr Pro Ser Ser Gln Ser Ser Pro Val Phe Pro Val Phe Pro
 20 25 30
 Val Ser Phe Met Ala Leu Ile Val Cys Xaa Leu Val Cys Cys
 35 40 45

<210> 1059
 <211> 134
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (130)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1059
 Met Ala Ser Ser Val Pro Ala Gly Gly His Thr Arg Ala Gly Gly Ile
 1 5 10 15
 Phe Leu Ile Gly Lys Leu Asp Leu Glu Ala Ser Leu Phe Lys Ser Phe
 20 25 30
 Gln Trp Leu Pro Phe Val Leu Arg Lys Lys Cys Asn Phe Phe Cys Trp
 35 40 45
 Asp Ser Ser Ala His Ser Leu Pro Leu His Pro Leu Ser Ala Ser Cys

534

50 55 60
 Ser Ala Pro Ala Cys His Ala Ser Asp Thr His Leu Leu Tyr Pro Ser
 65 70 75 80
 Thr Arg Ala Leu Cys Pro Ser Ile Phe Ala Trp Leu Val Ala Pro His
 85 90 95
 Ser Val Phe Arg Thr Asn Ala Pro Gly Pro Thr Pro Ser Ser Gln Ser
 100 105 110
 Ser Pro Val Phe Pro Val Phe Pro Val Ser Phe Met Ala Leu Ile Val
 115 120 125
 Cys Xaa Leu Val Cys Cys
 130

<210> 1060
 <211> 118
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (112)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1060
 Leu Val Asn Trp Ile Leu Lys Leu His Cys Leu Asn Leu Phe Ser Gly
 1 5 10 15
 Phe Pro Leu Tyr Leu Glu Lys Asn Ala Thr Ser Ser Ala Gly Thr His
 20 25 30
 Pro Leu Thr Ala Phe Pro Ser Thr Leu Ser Leu Pro His Ala Leu Pro
 35 40 45
 Leu Pro Ala Met Pro Pro Ile Leu Thr Phe Cys Thr Pro Ala Pro Val
 50 55 60
 Pro Ser Ala Pro Arg Ser Leu Pro Gly Trp Leu Leu Leu Thr Gln Cys
 65 70 75 80
 Ser Gly Gln Met Leu Leu Ala Leu Pro His Leu Ala Ser Leu Ala Arg
 85 90 95
 Ser Ser Leu Ser Ser Leu Phe His Ser Trp Leu Leu Leu Phe Val Xaa
 100 105 110
 Leu Cys Ala Val Asp Phe
 115

<210> 1061
 <211> 23
 <212> PRT
 <213> Homo sapiens

535

<400> 1061

Asn Leu Phe Ser Gly Phe Pro Leu Tyr Leu Glu Lys Asn Ala Thr Ser
 1 5 10 15

Ser Ala Gly Thr His Pro Leu
 20

<210> 1062

<211> 21

<212> PRT

<213> Homo sapiens

<400> 1062

Pro His Leu Ala Ser Leu Ala Arg Ser Ser Leu Ser Ser Leu Phe His
 1 5 10 15

Ser Trp Leu Leu Leu
 20

<210> 1063

<211> 286

<212> PRT

<213> Homo sapiens

<400> 1063

Met Ala Met Glu Gly Tyr Trp Arg Phe Leu Ala Leu Leu Gly Ser Ala
 1 5 10 15

Leu Leu Val Gly Phe Leu Ser Val Ile Phe Ala Leu Val Trp Val Leu
 20 25 30

His Tyr Arg Glu Gly Leu Gly Trp Asp Gly Ser Ala Leu Glu Phe Asn
 35 40 45

Trp His Pro Val Leu Met Val Thr Gly Phe Val Phe Ile Gln Gly Ile
 50 55 60

Ala Ile Ile Val Tyr Arg Leu Pro Trp Thr Trp Lys Cys Ser Lys Leu
 65 70 75 80

Leu Met Lys Ser Ile His Ala Gly Leu Asn Ala Val Ala Ala Ile Leu
 85 90 95

Ala Ile Ile Ser Val Val Ala Val Phe Glu Asn His Asn Val Asn Asn
 100 105 110

Ile Ala Asn Met Tyr Ser Leu His Ser Trp Val Gly Leu Ile Ala Val
 115 120 125

Ile Cys Tyr Leu Leu Gln Leu Leu Ser Gly Phe Ser Val Phe Leu Leu
 130 135 140

Pro Trp Ala Pro Leu Ser Leu Arg Ala Phe Leu Met Pro Ile His Val
 145 150 155 160

536

Tyr Ser Gly Ile Val Ile Phe Gly Thr Val Ile Ala Thr Ala Leu Met
 165 170 175
 Gly Leu Thr Glu Lys Leu Ile Phe Ser Leu Arg Asp Pro Ala Tyr Ser
 180 185 190
 Thr Phe Pro Pro Glu Gly Val Phe Val Asn Thr Leu Gly Leu Leu Ile
 195 200 205
 Leu Val Phe Gly Ala Leu Ile Phe Trp Ile Val Thr Arg Pro Gln Trp
 210 215 220
 Lys Arg Pro Lys Glu Pro Asn Ser Thr Ile Leu His Pro Asn Gly Gly
 225 230 235 240
 Thr Glu Gln Gly Ala Arg Gly Ser Met Pro Ala Tyr Ser Gly Asn Asn
 245 250 255
 Met Asp Lys Ser Asp Ser Glu Leu Asn Ser Glu Val Ala Ala Arg Lys
 260 265 270
 Arg Asn Leu Ala Leu Asp Glu Ala Gly Gln Arg Ser Thr Met
 275 280 285

<210> 1064

<211> 16

<212> PRT

<213> Homo sapiens

<400> 1064

Ala His Ala Ser Ala His Ala Ser Gly Gly Ala Glu Tyr Gly Ala Leu
 1 5 10 15

<210> 1065

<211> 116

<212> PRT

<213> Homo sapiens

<400> 1065

Gln Tyr Ser Gln Tyr Val Gln Ser Ala Gln Leu Gly Trp Thr Asp Ser
 1 5 10 15
 Cys His Met Leu Phe Val Thr Ala Ser Phe Arg Phe Phe Ser Leu Ser
 20 25 30
 Ala Ser Met Gly Ser Ala Phe Ser Pro Ser Ile Ser His Ala His Thr
 35 40 45
 Cys Leu Phe Trp Asn Cys His Leu Trp Asn Ser Asp Cys Asn Ser Thr
 50 55 60
 Tyr Gly Ile Asp Arg Glu Thr Asp Phe Phe Pro Glu Arg Ser Cys Ile
 65 70 75 80

537

Gln Tyr Ile Pro Ala Arg Arg Cys Phe Arg Lys Tyr Ala Trp Pro Ser
 85 90 95

Asp Pro Gly Val Arg Gly Pro His Phe Leu Asp Ser His Gln Thr Ala
 100 105 110

Met Glu Thr Ser
 115

<210> 1066
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 1066
 Ala Ser Met Gly Ser Ala Phe Ser Pro Ser Ile Ser His Ala His Thr
 1 5 10 15

Cys Leu Phe Trp Asn Cys His Leu Trp Asn Ser Asp Cys Asn Ser Thr
 20 25 30

Tyr Gly

<210> 1067
 <211> 119
 <212> PRT
 <213> Homo sapiens

<400> 1067
 Phe Val His Val Val Ala Arg Val Gly Trp His Gly Thr Ser Cys Ser
 1 5 10 15

Leu Phe Ser Ala Ser Ile Trp Met Lys Asn Gly Arg Ile Trp Leu Leu
 20 25 30

Arg Thr Phe Pro Leu Arg Ser Gly Asp Tyr Pro Lys Asn Glu Gly Pro
 35 40 45

Glu His Gln Asp Gln Lys Ala Lys Arg Ile Tyr Glu Asn Thr Phe Trp
 50 55 60

Arg Glu Cys Thr Val Cys Arg Ile Ser Gln Gly Lys Asn Gln Phe Leu
 65 70 75 80

Cys Gln Ser His Lys Cys Cys Cys Asn His Cys Ser Lys Asp Asp Asn
 85 90 95

Ser Arg Ile Asn Met Tyr Gly His Glu Lys Cys Ser Glu Arg Lys Arg
 100 105 110

Ser Pro Trp Lys Gln Lys Asp
 115

538

<210> 1068
<211> 32
<212> PRT
<213> Homo sapiens

<400> 1068
Ala Ser Ile Trp Met Lys Asn Gly Arg Ile Trp Leu Leu Arg Thr Phe
1 5 10 15
Pro Leu Arg Ser Gly Asp Tyr Pro Lys Asn Glu Gly Pro Glu His Gln
20 25 30

<210> 1069
<211> 43
<212> PRT
<213> Homo sapiens

<400> 1069
Pro Gly Arg Ala Gly Pro Ser Pro Gly Leu Ser Leu Gln Leu Pro Ala
1 5 10 15
Glu Pro Gly His Pro Ala Gly Asn Leu Ala Pro Leu Thr Ser Arg Pro
20 25 30
Gln Pro Leu Cys Arg Ile Pro Ala Val Pro Gly
35 40

<210> 1070
<211> 42
<212> PRT
<213> Homo sapiens

<400> 1070
Ala Arg Gly Arg Arg Gly Arg Leu Glu Leu Trp Glu Leu Cys Leu
1 5 10 15
Pro Leu Gly Cys Arg Arg Arg Arg Ser Leu Thr Met Ala Pro Gln Ser
20 25 30
Leu Pro Ser Ser Arg Met Ala Pro Leu Gly
35 40

<210> 1071
<211> 351
<212> PRT
<213> Homo sapiens

<400> 1071
Asn Gly Gln Ala Ser Thr Ala Lys Met Ser Ser Cys Leu Arg Ser Pro
1 5 10 15
Pro Thr Leu Ala Pro Leu Ser Leu Thr Ser Gly Ile Pro Val Gln Ser

539

20					25					30					
Trp	Cys	Gly	Ala	Ser	Ser	Gln	Leu	Leu	Gln	Gln	Ala	Val	Asp	Arg	Ala
		35					40					45			
Gln	Gln	Leu	Leu	Glu	Val	Ala	Leu	Val	Leu	Thr	Ile	Leu	Gln	Leu	Gln
		50				55					60				
Ala	Gly	Gln	His	Leu	Val	Leu	Ser	Leu	Gln	Ala	Gly	Gln	Cys	Pro	Ala
		65				70					75				80
Glu	Leu	Gly	Val	Leu	Thr	Val	Ala	Val	Pro	Ala	Gly	Gly	Gln	Glu	Asp
				85					90					95	
Ala	Gln	Cys	Leu	Gln	His	Leu	Leu	Thr	Gly	Ile	Met	Leu	Gly	Gln	Arg
			100					105					110		
Gln	Glu	Val	Gly	Arg	Asp	Leu	Ala	Pro	Ala	Leu	Phe	Pro	Gln	Ala	Trp
			115				120					125			
Gln	Glu	Val	Tyr	Leu	Ala	Ile	Leu	Leu	Gln	Leu	Leu	Trp	Gly	His	Leu
			130			135					140				
Leu	Gly	Gln	Leu	Ser	Leu	Leu	Leu	Gly	Glu	His	Leu	Leu	Arg	Asp	Gln
			145			150			155					160	
Val	Val	Glu	Gln	Cys	Asp	His	Ala	His	Gly	Glu	His	Leu	Arg	Ala	Leu
				165					170					175	
Leu	Leu	His	Gln	Gly	Pro	Gln	Asp	Leu	Gln	Pro	Pro	Glu	Leu	Gln	Glu
			180				185					190			
Leu	Pro	Leu	Gly	Ile	Gly	Glu	Val	Ala	Gln	Gln	Gly	Ala	Gln	Cys	Lys
			195				200					205			
Gln	Asp	Leu	Leu	Leu	Cys	Ser	Glu	Arg	Leu	Leu	Arg	Gly	Gln	Asp	Asp
			210			215					220				
Gln	Gln	Leu	Leu	Gln	Gly	Ser	Pro	Phe	Asp	Gly	Leu	His	Leu	Asp	Leu
			225			230			235					240	
Gly	Val	Ala	Gly	Lys	Gly	Ser	Ala	Gln	His	Lys	Arg	Ser	Ile	Leu	Leu
				245				250						255	
His	Glu	Gly	Leu	Cys	Ala	Val	Gln	Pro	Ile	Asp	His	His	Leu	Lys	Thr
			260				265						270		
Thr	Lys	Gly	Lys	Gln	Val	Leu	Arg	Ile	Val	His	Leu	Met	Asp	Ile	Ile
			275				280					285			
Phe	Lys	Ile	Lys	Glu	Arg	Ser	Asn	Leu	Leu	Phe	Gln	Thr	Gly	Ala	Gly
			290			295					300				
Thr	Ile	Glu	Leu	Val	Asp	Gln	Pro	Tyr	His	Asp	Leu	His	Val	Ser	Leu
			305			310			315					320	
Asn	Asp	Asn	Ile	Gln	Leu	Ile	Lys	Val	Phe	Leu	Gln	Phe	Leu	Asn	Gly
				325				330						335	

Ala Glu Glu Pro Leu Tyr Leu Ser Leu Pro Cys Leu Val Phe Leu
340 345 350

<400> 1072
Gln His Leu Val Leu Ser Leu Gln Ala Gly Gln Cys Pro Ala Glu Leu
1 5 10 15
Gly Val Leu Thr Val Ala Val Pro Ala Gly Gly Gln Glu Asp Ala Gln
20 25 30

```
<210> 1073
<211> 26
<212> PRT
<213> Homo sapiens
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```

<400> 1073
Gln Leu Ser Leu Leu Leu Gly Glu His Leu Leu Arg Asp Gln Val Val
 1             5             10             15
Glu Gln Cys Asp His Ala His Gly Glu His
 20             25

```

```
<210> 1074
<211> 32
<212> PRT
<213> Homo sapiens
```

<400> 1074
Gly Ser Pro Phe Asp Gly Leu His Leu Asp Leu Gly Val Ala Gly Lys
1 5 10 15
Gly Ser Ala Gln His Lys Arg Ser Ile Leu Leu His Glu Gly Leu Cys
20 25 30

```
<210> 1075
<211> 30
<212> PRT
<213> Homo sapiens
```

<400> 1075
His Leu Met Asp Ile Ile Phe Lys Ile Lys Glu Arg Ser Asn Leu Leu
1 5 10 15

541

Phe Gln Thr Gly Ala Gly Thr Ile Glu Leu Val Asp Gln Pro
 20 25 30

<210> 1076

<211> 126

<212> PRT

<213> Homo sapiens

<400> 1076

Asp Glu Pro Cys Pro Pro Pro Ala Ala Ser Cys Ala Pro Pro Ser Trp
 1 5 10 15

Arg Met Glu Leu Arg Thr Gly Ser Val Gly Ser Gln Ala Val Ala Arg
 20 25 30

Arg Met Asp Gly Asp Ser Arg Asp Gly Gly Gly Gly Lys Asp Ala Thr
 35 40 45

Gly Ser Glu Asp Tyr Glu Asn Leu Pro Thr Ser Ala Ser Val Ser Thr
 50 55 60

His Met Thr Ala Gly Ala Met Ala Gly Ile Leu Glu His Ser Val Met
 65 70 75 80

Tyr Pro Val Asp Ser Val Lys Thr Arg Met Gln Ser Leu Ser Pro Asp
 85 90 95

Pro Lys Ala Gln Tyr Thr Ser Ile Tyr Gly Ala Leu Lys Lys Ile Met
 100 105 110

Arg Thr Glu Ala Ser Gly Gly Pro Cys Glu Ala Ser Thr Ser
 115 120 125

<210> 1077

<211> 34

<212> PRT

<213> Homo sapiens

<400> 1077

Arg Met Glu Leu Arg Thr Gly Ser Val Gly Ser Gln Ala Val Ala Arg
 1 5 10 15

Arg Met Asp Gly Asp Ser Arg Asp Gly Gly Gly Gly Lys Asp Ala Thr
 20 25 30

Gly Ser

<210> 1078

<211> 27

<212> PRT

<213> Homo sapiens

<400> 1078

542

Pro Val Asp Ser Val Lys Thr Arg Met Gln Ser Leu Ser Pro Asp Pro
 1 5 10 15

Lys Ala Gln Tyr Thr Ser Ile Tyr Gly Ala Leu
 20 25

<210> 1079

<211> 424

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (152)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (314)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (359)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1079

Met Lys Leu Leu Gly Glu Cys Ser Ser Ser Ile Asp Ser Val Lys Arg
 1 5 10 15

Leu Glu His Lys Leu Lys Glu Glu Glu Glu Ser Leu Pro Gly Phe Val
 20 25 30

Asn Leu His Ser Thr Glu Thr Gln Thr Ala Gly Val Ile Asp Arg Trp
 35 40 45

Glu Leu Leu Gln Ala Gln Ala Leu Ser Lys Glu Leu Arg Met Lys Gln
 50 55 60

Asn Leu Gln Lys Trp Gln Gln Phe Asn Ser Asp Leu Asn Ser Ile Trp
 65 70 75 80

Ala Trp Leu Gly Asp Thr Glu Glu Glu Leu Glu Gln Leu Gln Arg Leu
 85 90 95

Glu Leu Ser Thr Asp Ile Gln Thr Ile Glu Leu Gln Ile Lys Lys Leu
 100 105 110

Lys Glu Leu Gln Lys Ala Val Asp His Arg Lys Ala Ile Ile Leu Ser
 115 120 125

Ile Asn Leu Cys Ser Pro Glu Phe Thr Gln Ala Asp Ser Lys Glu Ser
 130 135 140

Arg Asp Leu Gln Asp Arg Leu Xaa Gln Met Asn Gly Arg Trp Asp Arg
 145 150 155 160

543

Val Cys Ser Leu Leu Glu Glu Trp Arg Gly Leu Leu Gln Asp Ala Leu
 165 170 175
 Met Gln Cys Gln Gly Phe His Glu Met Ser His Gly Leu Leu Leu Met
 180 185 190
 Leu Glu Asn Ile Asp Arg Arg Lys Asn Glu Ile Val Pro Ile Asp Ser
 195 200 205
 Asn Leu Asp Ala Glu Ile Leu Gln Asp His His Lys Gln Leu Met Gln
 210 215 220
 Ile Lys His Glu Leu Leu Glu Ser Gln Leu Arg Val Ala Ser Leu Gln
 225 230 235 240
 Asp Met Ser Cys Gln Leu Leu Val Asn Ala Glu Gly Thr Asp Cys Leu
 245 250 255
 Glu Ala Lys Glu Lys Val His Val Ile Gly Asn Arg Leu Lys Leu Leu
 260 265 270
 Leu Lys Glu Val Ser Arg His Ile Lys Glu Leu Glu Lys Leu Leu Asp
 275 280 285
 Val Ser Ser Ser Gln Gln Asp Leu Ser Ser Trp Ser Ser Ala Asp Glu
 290 295 300
 Leu Asp Thr Ser Gly Ser Val Ser Pro Xaa Ser Gly Arg Ser Thr Pro
 305 310 315 320
 Asn Arg Gln Lys Thr Pro Arg Gly Lys Cys Ser Leu Ser Gln Pro Gly
 325 330 335
 Pro Ser Val Ser Ser Pro His Ser Arg Ser Thr Lys Gly Gly Ser Asp
 340 345 350
 Ser Ser Leu Ser Glu Pro Xaa Pro Gly Arg Ser Gly Arg Gly Phe Leu
 355 360 365
 Phe Arg Val Leu Arg Ala Ala Leu Pro Leu Gln Leu Leu Leu Leu
 370 375 380
 Leu Ile Gly Leu Ala Cys Leu Val Pro Met Ser Glu Glu Asp Tyr Ser
 385 390 395 400
 Cys Ala Leu Ser Asn Asn Phe Ala Arg Ser Phe His Pro Met Leu Arg
 405 410 415
 Tyr Thr Asn Gly Pro Pro Pro Leu
 420

<210> 1080

<211> 110

<212> PRT

<213> Homo sapiens

<400> 1080

544

Met Lys Leu Leu Gly Glu Cys Ser Ser Ser Ile Asp Ser Val Lys Arg
 1 5 10 15
 Leu Glu His Lys Leu Lys Glu Glu Glu Glu Ser Leu Pro Gly Phe Val
 20 25 30
 Asn Leu His Ser Thr Glu Thr Gln Thr Ala Gly Val Ile Asp Arg Trp
 35 40 45
 Glu Leu Leu Gln Ala Gln Ala Leu Ser Lys Glu Leu Arg Met Lys Gln
 50 55 60
 Asn Leu Gln Lys Trp Gln Gln Phe Asn Ser Asp Leu Asn Ser Ile Trp
 65 70 75 80
 Ala Trp Leu Gly Asp Thr Glu Glu Glu Leu Glu Gln Leu Gln Arg Leu
 85 90 95
 Glu Leu Ser Thr Asp Ile Gln Thr Ile Glu Leu Gln Ile Lys
 100 105 110

<210> 1081

<211> 136

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1081

Lys Leu Lys Glu Leu Gln Lys Ala Val Asp His Arg Lys Ala Ile Ile
 1 5 10 15
 Leu Ser Ile Asn Leu Cys Ser Pro Glu Phe Thr Gln Ala Asp Ser Lys
 20 25 30
 Glu Ser Arg Asp Leu Gln Asp Arg Leu Xaa Gln Met Asn Gly Arg Trp
 35 40 45
 Asp Arg Val Cys Ser Leu Leu Glu Glu Trp Arg Gly Leu Leu Gln Asp
 50 55 60
 Ala Leu Met Gln Cys Gln Gly Phe His Glu Met Ser His Gly Leu Leu
 65 70 75 80
 Leu Met Leu Glu Asn Ile Asp Arg Arg Lys Asn Glu Ile Val Pro Ile
 85 90 95
 Asp Ser Asn Leu Asp Ala Glu Ile Leu Gln Asp His His Lys Gln Leu
 100 105 110
 Met Gln Ile Lys His Glu Leu Leu Glu Ser Gln Leu Arg Val Ala Ser
 115 120 125
 Leu Gln Asp Met Ser Cys Gln Leu

545

130

135

<210> 1082

<211> 105

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1082

Gln	Asp	Met	Ser	Cys	Gln	Leu	Leu	Val	Asn	Ala	Glu	Gly	Thr	Asp	Cys
1				5					10					15	

Leu	Glu	Ala	Lys	Glu	Lys	Val	His	Val	Ile	Gly	Asn	Arg	Leu	Lys	Leu
		20					25						30		

Leu	Leu	Lys	Glu	Val	Ser	Arg	His	Ile	Lys	Glu	Leu	Glu	Lys	Leu	Leu
		35					40					45			

Asp	Val	Ser	Ser	Ser	Gln	Gln	Asp	Leu	Ser	Ser	Trp	Ser	Ser	Ala	Asp
	50					55					60				

Glu	Leu	Asp	Thr	Ser	Gly	Ser	Val	Ser	Pro	Xaa	Ser	Gly	Arg	Ser	Thr
65					70					75					80

Pro	Asn	Arg	Gln	Lys	Thr	Pro	Arg	Gly	Lys	Cys	Ser	Leu	Ser	Gln	Pro
			85						90					95	

Gly	Pro	Ser	Val	Ser	Ser	Pro	His	Ser
		100					105	

<210> 1083

<211> 73

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1083

Asp	Ser	Ser	Leu	Ser	Glu	Pro	Xaa	Pro	Gly	Arg	Ser	Gly	Arg	Gly	Phe
1				5					10					15	

Leu	Phe	Arg	Val	Leu	Arg	Ala	Ala	Leu	Pro	Leu	Gln	Leu	Leu	Leu	Leu
		20						25					30		

Leu	Leu	Ile	Gly	Leu	Ala	Cys	Leu	Val	Pro	Met	Ser	Glu	Glu	Asp	Tyr
		35					40					45			

Ser	Cys	Ala	Leu	Ser	Asn	Asn	Phe	Ala	Arg	Ser	Phe	His	Pro	Met	Leu
	50					55					60				

546

Arg Tyr Thr Asn Gly Pro Pro Pro Leu
65 70

<210> 1084

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1084

Gln Arg Phe Leu Pro Pro Gly Ser Cys Xaa Leu Ile Arg Gly Pro Gln
1 5 10 15

Cys Pro Arg Val Thr Asp Pro Thr Thr Gly Gln Ser Leu Asp Asp Ser
20 25 30

Arg Phe Gln Ile Gln Gln Thr Glu Asn Ile Ile Arg Ser Lys Thr Pro
35 40 45

Thr Gly Pro Glu Leu Asp Thr Ser Tyr Lys Gly Tyr
50 55 60

<210> 1085

<211> 215

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (64)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1085

Ser Ile Ser Ala Ser Arg Leu Glu Ser Ile Gly Thr Ile Ser Phe Phe
1 5 10 15

Leu Leu Ser Met Phe Ser Ser Ile Arg Ser Lys Pro Trp Leu Ile Ser
20 25 30

Trp Lys Pro Trp His Cys Ile Arg Ala Ser Cys Ser Arg Pro Arg His
35 40 45

Ser Ser Ser Arg Glu His Thr Arg Ser Gln Arg Pro Phe Ile Cys Xaa
50 55 60

Lys Arg Ser Cys Arg Ser Arg Leu Ser Leu Leu Ser Ala Trp Val Asn
65 70 75 80

Ser Gly Leu Gln Arg Leu Met Glu Arg Met Met Ala Leu Arg Trp Ser
85 90 95

547

Thr Ala Phe Trp Ser Ser Leu Ser Phe Leu Ile Trp Ser Ser Met Val
 100 105 110
 Trp Met Ser Val Leu Ser Ser Arg Arg Trp Ser Cys Ser Asn Ser Ser
 115 120 125
 Ser Val Ser Pro Ser Gln Ala Gln Met Leu Phe Lys Ser Glu Leu Asn
 130 135 140
 Cys Cys His Phe Trp Arg Phe Cys Phe Ile Leu Asn Ser Leu Leu Asn
 145 150 155 160
 Ala Trp Ala Trp Arg Ser Ser His Arg Ser Ile Thr Pro Ala Val Trp
 165 170 175
 Val Ser Val Leu Cys Arg Leu Thr Lys Pro Gly Arg Leu Ser Ser Ser
 180 185 190
 Ser Phe Ser Leu Cys Ser Ser Leu Phe Thr Glu Ser Ile Leu Leu Leu
 195 200 205
 His Ser Pro Ser Ser Phe Met
 210 215

<210> 1086
 <211> 35
 <212> PRT
 <213> Homo sapiens

<400> 1086
 Thr Ala Phe Trp Ser Ser Leu Ser Phe Leu Ile Trp Ser Ser Met Val
 1 5 10 15
 Trp Met Ser Val Leu Ser Ser Arg Arg Trp Ser Cys Ser Asn Ser Ser
 20 25 30
 Ser Val Ser
 35

<210> 1087
 <211> 26
 <212> PRT
 <213> Homo sapiens

<400> 1087
 Leu Leu Asn Ala Trp Ala Trp Arg Ser Ser His Arg Ser Ile Thr Pro
 1 5 10 15
 Ala Val Trp Val Ser Val Leu Cys Arg Leu
 20 25

<210> 1088
 <211> 171
 <212> PRT
 <213> Homo sapiens

548

<220>

<221> SITE

<222> (94)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1088

Leu Ala Arg His Val Leu Gln Arg Gly Tyr Ser Glu Leu Gly Phe Gln
 1 5 10 15

Gln Leu Met Leu Tyr Leu His Lys Leu Phe Val Met Val Leu Lys Tyr
 20 25 30

Leu Cys Ile Lys Val Arg Ile Asn Arg Asp Asn Phe Ile Phe Pro Ser
 35 40 45

Val Asn Val Leu Gln His Lys Lys Gln Thr Met Ala His Phe Met Glu
 50 55 60

Thr Leu Ala Leu His Gln Gly Ile Leu Gln Gln Ala Pro Pro Leu Leu
 65 70 75 80

Gln Gln Arg Ala His Ser Val Pro Ala Pro Ile His Leu Xaa Gln Ala
 85 90 95

Ile Leu Gln Val Pro Ala Leu Leu Ala Val Ser Leu Gly Glu Leu Arg
 100 105 110

Ala Ala Glu Ile Asp Gly Glu Asp Asp Gly Phe Ala Val Val His Ser
 115 120 125

Phe Leu Glu Leu Leu Glu Leu Phe Asp Leu Glu Leu Asp Gly Leu Asp
 130 135 140

Val Ser Ala Glu Phe Gln Thr Leu Glu Leu Phe Gln Leu Leu Leu Arg
 145 150 155 160

Val Pro Gln Pro Gly Pro Asp Ala Val Gln Val
 165 170

<210> 1089

<211> 28

<212> PRT

<213> Homo sapiens

<400> 1089

Tyr Ser Glu Leu Gly Phe Gln Gln Leu Met Leu Tyr Leu His Lys Leu
 1 5 10 15

Phe Val Met Val Leu Lys Tyr Leu Cys Ile Lys Val
 20 25

<210> 1090

<211> 29

<212> PRT

<213> Homo sapiens

549

<400> 1090

Val His Ser Phe Leu Glu Leu Leu Glu Leu Phe Asp Leu Glu Leu Asp
 1 5 10 15

Gly Leu Asp Val Ser Ala Glu Phe Gln Thr Leu Glu Leu
 20 25

<210> 1091

<211> 15

<212> PRT

<213> Homo sapiens

<400> 1091

Ala Met Val Cys Phe Leu Cys Trp Arg Thr Leu Thr Glu Gly Lys
 1 5 10 15

<210> 1092

<211> 97

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (73)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1092

Gly Ala Gly Val Gly Thr Ala Met Pro Arg Val Pro Gln Ser Ala Gly
 1 5 10 15

Gly Ala Val Thr Trp Trp Gly Val Gly Leu Ser Gln Pro Ser Ser Val
 20 25 30

Gln Gly Gly Ala Arg Pro Gly Thr Val Pro Gly Thr Pro Gly Pro Leu
 35 40 45

Pro Gly Leu Ser Pro Ala Pro Pro Pro Gln His Pro Pro Pro Leu Pro
 50 55 60

Lys Leu Phe Leu Leu Cys Leu Ser Xaa Ser Leu Pro Gln Asp Phe Ser
 65 70 75 80

Leu Leu Leu Cys Leu Ser Leu Asp Pro Cys Pro Ser Ser Thr Ser Asp
 85 90 95

Leu

<210> 1093

<211> 30

<212> PRT

<213> Homo sapiens

<400> 1093

550

Gly Thr Val Pro Gly Thr Pro Gly Pro Leu Pro Gly Leu Ser Pro Ala
 1 5 10 15

Pro Pro Pro Gln His Pro Pro Pro Leu Pro Lys Leu Phe Leu
 20 25 30

<210> 1094

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (83)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (136)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1094

Ala Pro Ser Arg Cys Arg Arg Ser Val Val Gln Val Pro Tyr Ser Ala
 1 5 10 15

Phe Ser Ser Cys Ser Trp Thr Pro Thr Ala Leu Arg Arg Gly Val Leu
 20 25 30

Leu Tyr Ala Gly Leu Ser Thr Ser Ser Ala Ser Lys Ala Gln Gly Trp
 35 40 45

His Cys Leu Gly Leu Glu Tyr Pro Ser Gly Ala Ile Met Glu Val Arg
 50 55 60

Gly Arg Gly Gly Asp Arg Tyr Ala Gln Gly Pro Ser Lys Cys Trp Arg
 65 70 75 80

Gly Cys Xaa Leu Val Gly Ser Gly Ser Val Thr Ala Ile Leu Cys Pro
 85 90 95

Gly Trp Gly Lys Ala Trp Asp Ser Ala Arg His Pro Arg Thr Pro Ser
 100 105 110

Arg Leu Val Ser Cys Ser Thr Ala Ser Thr Pro Pro Thr Pro Ala Gln
 115 120 125

Ala Val Ser Pro Leu Pro Leu Xaa Phe Pro Ala Pro Gly Leu Leu Ser
 130 135 140

Ser Pro Leu Pro Leu Leu Gly Pro Leu Pro Phe Leu Tyr Leu
 145 150 155

<210> 1095

<211> 37

<212> PRT

<213> Homo sapiens

551

<400> 1095

Thr Ala Leu Arg Arg Gly Val Leu Leu Tyr Ala Gly Leu Ser Thr Ser
 1 5 10 15

Ser Ala Ser Lys Ala Gln Gly Trp His Cys Leu Gly Leu Glu Tyr Pro
 20 25 30

Ser Gly Ala Ile Met
 35

<210> 1096

<211> 33

<212> PRT

<213> Homo sapiens

<400> 1096

Ala Ile Leu Cys Pro Gly Trp Gly Lys Ala Trp Asp Ser Ala Arg His
 1 5 10 15

Pro Arg Thr Pro Ser Arg Leu Val Ser Cys Ser Thr Ala Ser Thr Pro
 20 25 30

Pro

<210> 1097

<211> 112

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (67)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1097

Pro Pro Val Phe Met Ala Ser His Arg Pro Xaa Gly Met Glu Pro Gly
 1 5 10 15

Glu Trp Arg Phe Val Leu Val His Ile Ala Phe Xaa Cys Ala Trp Asp
 20 25 30

Leu Val Cys Glu His Val Ser Val Cys Ser Gln Val Arg Gly Arg Gly
 35 40 45

552

Arg Ala Gly Val Gln Gly Glu Ala Glu Glu Lys Arg Glu Val Leu Gly
 50 55 60

Gln Gly Xaa Arg Glu Ala Glu Glu Lys Gln Leu Gly Gln Gly Trp Gly
 65 70 75 80

Val Leu Arg Arg Trp Ser Arg Arg Gln Ala Trp Lys Gly Ser Trp Gly
 85 90 95

Ala Trp His Cys Pro Arg Pro Cys Pro Thr Leu Asp Arg Gly Trp Leu
 100 105 110

<210> 1098
 <211> 29
 <212> PRT
 <213> Homo sapiens

<400> 1098
 His Val Ser Val Cys Ser Gln Val Arg Gly Arg Gly Arg Ala Gly Val
 1 5 10 15

Gln Gly Glu Ala Glu Glu Lys Arg Glu Val Leu Gly Gln
 20 25

<210> 1099
 <211> 56
 <212> PRT
 <213> Homo sapiens

<400> 1099
 Met Lys Leu Leu Ile Cys Gly Asn Tyr Leu Ala Pro Ser His Ser Glu
 1 5 10 15

Ser Ser Arg Arg Cys Cys Leu Leu Cys Phe Tyr Pro Leu Cys Leu Glu
 20 25 30

Ile Asn Phe Gly Met Lys Val Phe Leu Ser Met Pro Phe Leu Val Leu
 35 40 45

Phe Gln Ser Leu Ile Gln Glu Asp
 50 55

<210> 1100
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 1100
 Phe Ser Ser Pro Gln Gly Leu Lys Phe Arg Ser Lys Ser Ser Leu Ala
 1 5 10 15

Asn Tyr Leu His Lys Asn Gly Glu Thr Ser Leu Lys Pro Glu Asp Phe

553

20 25 30
 Asp Phe Thr Val Leu Ser Lys Arg Gly Ile Lys Ser Arg Tyr Lys Asp
 35 40 45
 Cys Ser
 50

 <210> 1101
 <211> 137
 <212> PRT
 <213> Homo sapiens

 <400> 1101
 Glu Leu Leu Cys Tyr Ile Cys Trp Lys Asn Thr Gly Leu Phe Ser Phe
 1 5 10 15
 Phe Leu Ser Val Phe Arg Gly Met Val Ser Ser Val Lys Ser Phe Leu
 20 25 30
 Val Gly Glu Gln Leu Leu Ser Ile Ser Glu Pro Arg Phe Lys Met Ser
 35 40 45
 Val Cys Lys Cys Ser Phe Leu Ser Thr Thr Ser Thr Phe Val Pro Ile
 50 55 60
 Ser Ser Asp Ser Lys Lys Val Ser Ser Tyr Phe Ser Leu Cys Ser Glu
 65 70 75 80
 Ser Leu Ala Glu Gln Asn Leu Phe Met Met Pro Glu Val Phe Cys Ser
 85 90 95
 Glu Gln Lys Phe Asp Pro Glu Leu Asn Asp Leu Ser Phe Phe Phe Thr
 100 105 110
 Arg Leu Phe Ser Ser Leu Val Thr Leu Arg Val Ser Pro His Ala Pro
 115 120 125
 Ala Ser Glu Met Gln Thr Val Leu Ser
 130 135

 <210> 1102
 <211> 36
 <212> PRT
 <213> Homo sapiens

 <400> 1102
 Thr Phe Val Pro Ile Ser Ser Asp Ser Lys Lys Val Ser Ser Tyr Phe
 1 5 10 15
 Ser Leu Cys Ser Glu Ser Leu Ala Glu Gln Asn Leu Phe Met Met Pro
 20 25 30
 Glu Val Phe Cys
 35

554

<210> 1103
 <211> 271
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (112)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (231)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1103

Arg	Ile	Leu	Leu	Val	Lys	Tyr	Ser	Ala	Asn	Glu	Glu	Asn	Lys	Tyr	Asp
1				5					10					15	
Tyr	Leu	Pro	Thr	Thr	Val	Asn	Val	Cys	Ser	Glu	Leu	Val	Lys	Leu	Val
			20					25					30		
Phe	Cys	Val	Leu	Val	Ser	Phe	Cys	Val	Ile	Lys	Lys	Asp	His	Gln	Ser
		35					40					45			
Arg	Asn	Leu	Lys	Tyr	Ala	Ser	Trp	Lys	Glu	Phe	Ser	Asp	Phe	Met	Lys
	50					55					60				
Trp	Ser	Ile	Pro	Ala	Phe	Leu	Tyr	Phe	Leu	Asp	Asn	Leu	Ile	Val	Phe
65				70					75					80	
Tyr	Val	Leu	Ser	Tyr	Leu	Gln	Pro	Ala	Met	Ala	Val	Ile	Phe	Ser	Asn
			85					90						95	
Phe	Ser	Ile	Ile	Thr	Thr	Ala	Leu	Leu	Phe	Arg	Ile	Val	Leu	Lys	Xaa
			100					105					110		
Arg	Leu	Asn	Trp	Ile	Gln	Trp	Ala	Ser	Leu	Leu	Thr	Leu	Phe	Leu	Ser
	115					120						125			
Ile	Val	Ala	Leu	Thr	Ala	Gly	Thr	Lys	Thr	Leu	Gln	His	Asn	Leu	Ala
	130					135					140				
Gly	Arg	Gly	Phe	His	His	Asp	Ala	Phe	Phe	Ser	Pro	Ser	Asn	Ser	Cys
145				150						155				160	
Leu	Leu	Phe	Arg	Asn	Glu	Cys	Pro	Arg	Lys	Asp	Asn	Cys	Thr	Ala	Lys
			165						170					175	
Glu	Trp	Thr	Phe	Pro	Glu	Ala	Lys	Trp	Asn	Thr	Thr	Ala	Arg	Val	Phe
		180						185					190		
Ser	His	Ile	Arg	Leu	Gly	Met	Gly	His	Val	Leu	Ile	Ile	Val	Gln	Cys
	195					200						205			
Phe	Ile	Ser	Ser	Met	Ala	Asn	Ile	Tyr	Asn	Glu	Lys	Ile	Leu	Lys	Glu
	210					215					220				

555

Gly Asn Gln Leu Thr Glu Xaa Ile Phe Ile Gln Asn Ser Lys Leu Tyr
 225 230 235 240

Phe Phe Gly Ile Leu Phe Asn Gly Leu Thr Leu Gly Leu Gln Arg Ser
 245 250 255

Asn Arg Asp Gln Ile Lys Asn Cys Gly Phe Phe Tyr Gly His Ser
 260 265 270

<210> 1104

<211> 30

<212> PRT

<213> Homo sapiens

<400> 1104

Thr Val Asn Val Cys Ser Glu Leu Val Lys Leu Val Phe Cys Val Leu
 1 5 10 15

Val Ser Phe Cys Val Ile Lys Lys Asp His Gln Ser Arg Asn
 20 25 30

<210> 1105

<211> 31

<212> PRT

<213> Homo sapiens

<400> 1105

Leu Ile Val Phe Tyr Val Leu Ser Tyr Leu Gln Pro Ala Met Ala Val
 1 5 10 15

Ile Phe Ser Asn Phe Ser Ile Ile Thr Thr Ala Leu Leu Phe Arg
 20 25 30

<210> 1106

<211> 27

<212> PRT

<213> Homo sapiens

<400> 1106

Phe Phe Ser Pro Ser Asn Ser Cys Leu Leu Phe Arg Asn Glu Cys Pro
 1 5 10 15

Arg Lys Asp Asn Cys Thr Ala Lys Glu Trp Thr
 20 25

<210> 1107

<211> 28

<212> PRT

<213> Homo sapiens

<400> 1107

Tyr Phe Phe Gly Ile Leu Phe Asn Gly Leu Thr Leu Gly Leu Gln Arg
 1 5 10 15

556

Ser Asn Arg Asp Gln Ile Lys Asn Cys Gly Phe Phe
20 25

<210> 1108

<211> 94

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1108

Asn Ser Val Pro Asn Leu Gln Thr Leu Ala Val Leu Thr Glu Ala Ile
1 5 10 15

Gly Pro Glu Pro Ala Ile Pro Arg Xaa Pro Arg Glu Pro Pro Val Ala
20 25 30

Thr Ser Thr Pro Ala Thr Pro Ser Ala Gly Pro Gln Pro Leu Pro Thr
35 40 45

Gly Thr Val Leu Val Pro Gly Gly Pro Ala Pro Pro Cys Leu Gly Glu
50 55 60

Ala Trp Ala Leu Leu Leu Pro Pro Cys Arg Pro Ser Leu Thr Ser Cys
65 70 75 80

Phe Trp Ser Pro Arg Pro Ser Pro Trp Lys Glu Thr Gly Val
85 90

<210> 1109

<211> 64

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1109

Val Thr Ala Gly Arg Val Gly Gly Gly Gly Pro Met Pro Pro Gln Gly
1 5 10 15

Lys Val Gly Gln Asp Pro Gln Gly Pro Ala Arg Ser Arg Leu Gly Gly
20 25 30

Ala Gly Ala Arg Gln Arg Val Trp Gln Val Trp Thr Trp Gln Gln Ala
35 40 45

Ala Pro Gly Gly Xaa Gly Gly Trp Arg Ala Leu Gly Gln Trp Pro Gln
50 55 60

557

<210> 1110
<211> 26
<212> PRT
<213> Homo sapiens

<400> 1110
Ser Thr Pro Ala Thr Pro Ser Ala Gly Pro Gln Pro Leu Pro Thr Gly
1 5 10 15
Thr Val Leu Val Pro Gly Gly Pro Ala Pro
20 25

<210> 1111
<211> 19
<212> PRT
<213> Homo sapiens

<400> 1111
Gln Asp Pro Gln Gly Pro Ala Arg Ser Arg Leu Gly Gly Ala Gly Ala
1 5 10 15

Arg Gln Arg

<210> 1112
<211> 40
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1112
Ala Leu Gln Leu Ala Phe Tyr Pro Asp Ala Val Glu Glu Trp Leu Glu
1 5 10 15

Glu Asn Val His Pro Ser Leu Gln Arg Leu Gln Xaa Leu Leu Gln Asp
20 25 30

Leu Ser Glu Val Ser Ala Pro Pro
35 40

<210> 1113
<211> 30
<212> PRT
<213> Homo sapiens

<400> 1113
Cys His Pro Pro Ala Leu Ala Gly Thr Leu Leu Arg Thr Pro Glu Gly

558

1 5 10 15
 Arg Ala His Ala Arg Gly Leu Leu Leu Glu Ala Gly Gly Ala
 20 25 30

 <210> 1114
 <211> 59
 <212> PRT
 <213> Homo sapiens

 <400> 1114
 Gly Ser Ser Ser Thr Arg Ser Trp Phe Ser Thr Ser Ser Pro Gln Arg
 1 5 10 15
 Ser Ala Ser Trp His Ser Gly Ala Pro Ser Cys Arg Ser Trp Arg Leu
 20 25 30
 Pro Cys Ser Trp Leu Ser Thr Arg Met Pro Trp Arg Ser Gly Trp Arg
 35 40 45
 Lys Thr Cys Thr Pro Ala Cys Ser Gly Cys Lys
 50 55

<210> 1115
 <211> 83
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (24)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1115
 Ala Ser Thr Leu Gln Pro Ser Leu Ser Pro Ser Ser Pro Pro Leu Xaa
 1 5 10 15
 Pro Pro Val Glu Thr Ala Val Xaa Ser Arg Ala Leu Arg Arg Glu Gly
 20 25 30
 Ala Gly Ser Phe Pro Gly Ser Asn Ile Leu Ala Leu Val Thr Gln Val
 35 40 45
 Ser Leu His Leu Arg Ser Ser Val Asp Ala Leu Leu Glu Gly Asn Arg
 50 55 60
 Tyr Val Thr Gly Trp Phe Ser Pro Tyr His Arg Gln Arg Lys Leu Ile
 65 70 75 80

His Pro Val

<210> 1116
<211> 292
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (15)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (36)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (39)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (40)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (45)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (91)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (255)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (256)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

560

<221> SITE

<222> (257)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (258)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1116

Pro Leu Gly Pro Glu Lys Ala Gly Leu Ala Xaa Pro Leu Val Xaa His
 1 5 10 15

Ala Ala Arg Pro Cys Pro Ser Thr Ser Leu Gln Ser Gln Cys Ser Pro
 20 25 30

Ser Leu Xaa Xaa Glu Pro Xaa Xaa Pro Pro Arg Ser Xaa Val Ile Ser
 35 40 45

Gly Gly Phe Asp Glu Asp Val Lys Ala Lys Val Glu Asn Leu Leu Gly
 50 55 60

Ile Ser Ser Leu Glu Lys Thr Asp Pro Val Arg Gln Ala Pro Cys Ser
 65 70 75 80

Pro Pro Cys Pro Leu Leu Pro Leu Pro Phe Xaa Arg Pro Trp Arg Gln
 85 90 95

Leu Phe Ser Ala Gly Leu Ser Ala Gly Arg Gly Pro Ala Pro Ser Leu
 100 105 110

Ala Ala Thr Ser Leu Pro Leu Ser His Lys Ser Ala Ser Ile Cys Ala
 115 120 125

Ala Leu Trp Met Arg Cys Trp Arg Ala Thr Gly Met Ser Leu Ala Gly
 130 135 140

Ser Ala Pro Thr Thr Ala Ser Gly Ser Ser Ser Thr Arg Ser Trp Phe
 145 150 155 160

Ser Thr Ser Ser Pro Gln Arg Ser Ala Ser Trp His Ser Gly Ala Pro
 165 170 175

Ser Cys Arg Ser Trp Arg Leu Pro Cys Ser Trp Leu Ser Thr Arg Met
 180 185 190

Pro Trp Arg Ser Gly Trp Arg Lys Thr Cys Thr Pro Ala Cys Ser Gly
 195 200 205

Cys Lys Leu Cys Cys Arg Thr Ser Ala Arg Cys Leu Pro Pro Arg Cys
 210 215 220

His Pro Pro Ala Leu Ala Gly Thr Leu Leu Arg Thr Pro Glu Gly Arg
 225 230 235 240

Ala His Ala Arg Gly Leu Leu Leu Glu Ala Gly Gly Ala Leu Xaa Xaa
 245 250 255

Gln Gln Cys Leu Ala His Thr Gln Phe Leu Arg Ala Leu Gly Ser Pro
275 280 285

Trp Gly Arg Asp
290

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<210> 1117
<211> 235
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (52)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (164)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (209)
<223> Xaa equals any of the naturally occurring L-amino acids

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<220>
<221> SITE
<222> (210)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (211)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 1117
Phe Gln Glu Asp Leu Met Lys Met Leu Lys Arg Lys Trp Arg Thr Phe
1 5 10 15

Ser Gly Phe Pro Ala Trp Lys Lys Arg Thr Leu Leu Gly Lys His Pro
20 25 30

Ala Ala Leu Pro Val Pro Phe Phe Pro Ser Pro Ser Pro Ala Arg Gly
35 40 45

Asp Ser Cys Xaa Gln Gln Gly Ser Pro Gln Gly Gly Gly Arg Leu Leu
50 55 60

Pro	Trp	Gln	Gln	His	Pro	Cys	Pro	Cys	His	Thr	Ser	Gln	Pro	Pro	Ser
65					70					75					80

Ala Gln Leu Cys Gly Cys Ala Ala Gly Gly Gln Gln Val Cys His Trp
85 90 95

562

Leu Val Gln Pro Leu Pro Pro Pro Ala Glu Ala His Pro Pro Gly His
 100 105 110

Gly Ser Ala His Pro Ala Arg Ser Ala Gln Pro Pro Gly Thr Val Glu
 115 120 125

His Pro Arg Ala Gly Ala Gly Gly Cys Pro Ala Ala Gly Phe Leu Pro
 130 135 140

Gly Cys Arg Gly Gly Val Ala Gly Gly Lys Arg Ala Pro Gln Pro Ala
 145 150 155 160

Ala Ala Ala Xaa Ser Ala Ala Gly Pro Gln Arg Gly Val Cys Pro Pro
 165 170 175

Ala Ala Thr His Gln Pro Trp Gln Gly Arg Cys Ser Gly Pro Leu Arg
 180 185 190

Gly Glu Leu Met Pro Gly Gly Ser Cys Trp Arg Leu Gly Gly Leu Cys
 195 200 205

Xaa Xaa Xaa Trp Pro Gly Gln Tyr Gly Pro Arg Gly Arg Arg Ala Leu
 210 215 220

Trp Pro Ser Ser Val Leu Pro Thr Leu Ser Ser
 225 230 235

<210> 1118

<211> 241

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (151)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (197)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (198)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (202)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (203)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (206)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (207)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (227)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1118

Ala	Leu	Pro	Ser	Gly	Val	Leu	Ser	Asn	Val	Pro	Ala	Arg	Ala	Gly	Gly
1				5					10					15	

Trp	Gln	Arg	Gly	Gly	Arg	His	Leu	Ala	Glu	Val	Leu	Gln	Gln	Ser	Leu
	20						25						30		

Gln	Pro	Leu	Gln	Ala	Gly	Val	His	Val	Phe	Leu	Gln	Pro	Leu	Leu	His
	35						40					45			

Gly	Ile	Arg	Val	Glu	Ser	Gln	Leu	Gln	Gly	Ser	Leu	Gln	Leu	Leu	His
	50					55					60				

Glu	Gly	Ala	Pro	Leu	Cys	Gln	Glu	Ala	Glu	Arg	Cys	Gly	Leu	Asp	Val
65					70					75				80	

Leu	Asn	His	Asp	Arg	Val	Asp	Glu	Leu	Pro	Leu	Ala	Val	Val	Gly	Ala
			85						90					95	

Glu	Pro	Ala	Ser	Asp	Ile	Pro	Val	Ala	Leu	Gln	Gln	Arg	Ile	His	Arg
		100						105					110		

Ala	Ala	Gln	Met	Glu	Ala	Asp	Leu	Cys	Asp	Lys	Gly	Lys	Asp	Val	Ala
		115					120					125			

Ala	Arg	Glu	Gly	Ala	Gly	Pro	Leu	Pro	Ala	Glu	Ser	Pro	Ala	Glu	Asn
	130					135					140				

Ser	Cys	Leu	His	Gly	Arg	Xaa	Lys	Gly	Arg	Gly	Arg	Arg	Gly	Gln	Gly
145					150					155				160	

Gly	Leu	Gln	Gly	Ala	Cys	Leu	Thr	Gly	Ser	Val	Phe	Ser	Arg	Leu	Glu
			165						170					175	

Ile	Pro	Arg	Arg	Phe	Ser	Thr	Phe	Ala	Leu	Thr	Ser	Ser	Ser	Asn	Pro
			180					185						190	

Pro	Glu	Ile	Thr	Xaa	Xaa	Arg	Gly	Gly	Xaa	Xaa	Gly	Ser	Xaa	Xaa	Arg
		195					200					205			

Glu	Gly	Leu	His	Trp	Asp	Cys	Arg	Leu	Val	Leu	Gly	His	Gly	Arg	Ala
	210					215						220			

564

Ala Trp Xaa Thr Asn Gly Gln Ala Asn Pro Ala Phe Ser Gly Pro Lys
 225 230 235 240

Gly

<210> 1119

<211> 29

<212> PRT

<213> Homo sapiens

<400> 1119

Arg Gln Leu Phe Ser Ala Gly Leu Ser Ala Gly Arg Gly Pro Ala Pro
 1 5 10 15

Ser Leu Ala Ala Thr Ser Leu Pro Leu Ser His Lys Ser
 20 25

<210> 1120

<211> 28

<212> PRT

<213> Homo sapiens

<400> 1120

Glu Leu Pro Leu Ala Val Val Gly Ala Glu Pro Ala Ser Asp Ile Pro
 1 5 10 15

Val Ala Leu Gln Gln Arg Ile His Arg Ala Ala Gln
 20 25

<210> 1121

<211> 27

<212> PRT

<213> Homo sapiens

<400> 1121

Gln Pro Pro Gly Thr Val Glu His Pro Arg Ala Gly Ala Gly Gly Cys
 1 5 10 15

Pro Ala Ala Gly Phe Leu Pro Gly Cys Arg Gly
 20 25

<210> 1122

<211> 17

<212> PRT

<213> Homo sapiens

<400> 1122

Ser Val Phe Glu Arg Thr Asn Glu Phe Arg Asp Val Leu Trp Ser Ser
 1 5 10 15

Ile

565

<210> 1123
 <211> 97
 <212> PRT
 <213> Homo sapiens

<400> 1123

Gly	Val	Val	Gln	Val	Thr	Phe	Met	Ser	Ser	Val	Ser	Arg	Val	Thr	Trp
1				5					10					15	
Gly	Cys	Gln	Pro	Ser	Ile	Cys	Pro	Gly	Ala	Pro	Pro	Ala	Ala	Ala	Leu
		20						25					30		
Ala	Gly	Gly	Leu	Arg	Leu	Leu	Phe	Glu	Arg	Glu	Leu	Phe	Gly	Leu	Pro
	35						40					45			
Val	Ser	Ser	Pro	Leu	Ile	Cys	Ser	Phe	Leu	Glu	His	His	Pro	Arg	Thr
	50					55					60				
Ser	Pro	Pro	Pro	Ser	Asp	Cys	Glu	Leu	Leu	Glu	Gly	Arg	Ser	Cys	Val
	65				70					75					80
Leu	Leu	Phe	Ile	Phe	Leu	Ser	Pro	Glu	Pro	Cys	Thr	Asp	Pro	Gly	Met
			85						90					95	

Trp

<210> 1124
 <211> 101
 <212> PRT
 <213> Homo sapiens

<400> 1124

Ser	Lys	Gln	Ile	His	Ser	Phe	Val	His	Ser	Phe	Ile	His	Leu	Phe	Asn
1				5					10					15	
Thr	His	Leu	Leu	Ser	Thr	Tyr	His	Ile	Pro	Gly	Ser	Val	Gln	Gly	Ser
		20						25					30		
Gly	Asp	Arg	Lys	Met	Asn	Arg	Arg	Thr	Gln	Leu	Leu	Pro	Ser	Arg	Ser
	35					40						45			
Ser	Gln	Ser	Asp	Gly	Gly	Gly	Asp	Val	Leu	Gly	Trp	Cys	Ser	Lys	Lys
	50				55						60				
Glu	Gln	Ile	Arg	Gly	Glu	Glu	Thr	Gly	Arg	Pro	Asn	Ser	Ser	Leu	Ser
	65				70					75				80	
Lys	Arg	Ser	Leu	Arg	Pro	Pro	Ala	Arg	Ala	Ala	Ala	Gly	Gly	Ala	Pro
			85						90					95	

Gly Gln Met Leu Gly
 100

566

<210> 1125

<211> 28

<212> PRT

<213> Homo sapiens

<400> 1125

Val Thr Trp Gly Cys Gln Pro Ser Ile Cys Pro Gly Ala Pro Pro Ala
 1 5 10 15

Ala Ala Leu Ala Gly Gly Leu Arg Leu Leu Phe Glu
 20 25

<210> 1126

<211> 23

<212> PRT

<213> Homo sapiens

<400> 1126

Glu Gln Ile Arg Gly Glu Glu Thr Gly Arg Pro Asn Ser Ser Leu Ser
 1 5 10 15

Lys Arg Ser Leu Arg Pro Pro
 20

<210> 1127

<211> 130

<212> PRT

<213> Homo sapiens

<400> 1127

Gln Trp Glu His Leu Leu Leu Leu Pro His Leu Leu Arg Gly Ala His
 1 5 10 15

Arg Asp Pro Gly Asp Ile Leu Pro Leu Ala Pro Arg Ser Glu Cys Arg
 20 25 30

Ala Asn Ser Ile Lys Glu Tyr Gln Lys Ser Ile Trp Lys Val Tyr Val
 35 40 45

Val Arg Leu Arg Leu Leu Lys Pro Gln Pro Asn Ile Ile Pro Thr Val
 50 55 60

Lys Lys Ile Val Leu Leu Ala Gly Trp Ala Leu Phe Leu Phe Leu Ala
 65 70 75 80

Tyr Lys Val Ser Lys Thr Asp Arg Glu Tyr Gln Glu Tyr Asn Pro Tyr
 85 90 95

Glu Val Leu Asn Leu Asp Pro Gly Ala Thr Val Ala Glu Ile Lys Lys
 100 105 110

Gln Tyr Arg Leu Leu Ser Leu Lys Tyr His Pro Asp Lys Gly Gly Asp
 115 120 125

Glu Val
 130

567

<210> 1128
 <211> 65
 <212> PRT
 <213> Homo sapiens

<400> 1128
 Glu Glu Arg Gly Gly Gly Gly Ala Met Ala Gly Gln Gln Phe Gln
 1 5 10 15
 Tyr Asp Asp Ser Gly Asn Thr Phe Phe Tyr Phe Leu Thr Ser Phe Val
 20 25 30
 Gly Leu Ile Val Ile Pro Ala Thr Tyr Tyr Leu Trp Pro Arg Asp Gln
 35 40 45
 Asn Ala Glu Gln Ile Arg Leu Lys Asn Ile Arg Lys Val Tyr Gly Arg
 50 55 60
 Cys
 65

<210> 1129
 <211> 220
 <212> PRT
 <213> Homo sapiens

<400> 1129
 Arg Leu Tyr Thr Gly Cys Val Ile Phe Asp Leu Val Ser Asn Arg Ala
 1 5 10 15
 Leu Ser Phe Arg Cys Met Leu Cys Cys Asn Ser Cys His Ser Ala Ser
 20 25 30
 Ser Ser Leu Phe Cys Phe Ser Ser Cys Ser Leu Ser Glu Ser Leu Ser
 35 40 45
 Leu Pro Ser Ser Phe Ser Leu Trp Glu Ser Leu Leu Val Ser Ser Ser
 50 55 60
 Ser Glu Ser Leu Pro Leu Ser Glu Thr Ser Ser Ser Ser Ser Phe Thr
 65 70 75 80
 Ala Ala Ser Phe Pro Thr Thr Pro Phe Ala Cys Phe Cys Phe Cys Cys
 85 90 95
 Phe Asp Cys Gly Asn Ser Thr Gly Val Gly Phe Phe Phe Lys Gly Phe
 100 105 110
 Phe Phe Phe Asp Leu Ala Val Phe Leu Gly Pro Leu Leu Phe Cys Cys
 115 120 125
 His Pro Pro Phe Val Leu Phe Leu Leu Val Ser Pro Cys Pro Ser Ser
 130 135 140
 Ala Gly Cys Ser Ser Ala Ala Gln Met Asp Cys Ser Phe Ser Asn Thr

145					150					155					160
Ser	Ala	Ile	Val	Cys 165	Leu	Val	Asn	Leu	Thr 170	Asn	Thr	Val	Thr	Lys 175	Asp
Pro	Thr	Val	Met 180	Leu	Leu	Leu	Ser	Ser 185	Ser	Ser	Asn	Thr	Cys 190	Asp	Phe
Ile	Ser	Met 195	Val	Thr	Tyr	Gly	Lys 200	Leu	Pro	Arg	Thr	Ala 205	Ile	Thr	Ser
Ser	Tyr 210	Phe	Ser	Ser	Ser	Arg 215	Lys	Cys	Ser	Arg	Val 220				

<400> 1130
Tyr Gln Lys Ser Ile Trp Lys Val Tyr Val Val Arg Leu Arg Leu Leu
1 5 10 15

Ala Gly Trp
35

<400> 1131
Cys His Pro Pro Phe Val Leu Phe Leu Leu Val Ser Pro Cys Pro Ser
1 5 10 15

Thr Ser Ala
35

<400> 1132
Gly Thr Ser Leu Asp Ala Ala Ala Thr Ala Ala Ser Leu Ser Pro Arg
1 5 10 15

Gly Cys Arg Leu Arg Thr Pro Ser Ser Asp
20 25

569

<210> 1133

<211> 99

<212> PRT

<213> Homo sapiens

<400> 1133

Gln Ile Gln Arg His Thr Arg Ala Pro Lys Gln Leu Ile Pro Leu Met
 1 5 10 15

Thr Pro Arg Arg Ser Leu Arg Asp His Pro Gln Ala Gln Thr Ser Arg
 20 25 30

Gln Thr Pro Arg Pro Ser Ser His Leu Val Phe Met Arg Met Thr Pro
 35 40 45

Ser Ser Met Met Asn Thr Pro Ser Gly Asn Gly Gly Cys Trp Ser Gln
 50 55 60

Leu Cys Cys Ser Ser Gln Ala Ser Ser Ser Ser Pro Val Ala Ser Ala
 65 70 75 80

Gly Ser Cys Pro Gly Tyr Ala Gly Ile Ile Ala Gly Glu Ser Ile Arg
 85 90 95

Asn Arg Ser

<210> 1134

<211> 27

<212> PRT

<213> Homo sapiens

<400> 1134

Pro Arg Arg Ser Leu Arg Asp His Pro Gln Ala Gln Thr Ser Arg Gln
 1 5 10 15

Thr Pro Arg Pro Ser Ser His Leu Val Phe Met
 20 25

<210> 1135

<211> 129

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1135

Thr His Pro Pro Glu Thr Gly Ala Val Gly Arg Ser Cys Ala Val His
 1 5 10 15

His Arg His His His Pro His Gln Trp Gln Val Gln Ala Ala Val Pro

20

30

Leu Lys Leu Ser Pro Leu Leu Arg Gln Lys Val Lys His Cys Gly Leu
115 120 125

Leu Cys Leu Pro Ser Leu Ala Arg Leu Phe Glu Gly Met Gln Glu Ala

571

35 40 45
 Gly His Gly Glu Leu Ala Gly Gly Leu Val Phe Gly Cys Pro Ala Gly
 50 55 60
 Cys Gln Leu Leu Phe Leu Met Asp Ser Pro Ala Met Ile Pro Ala
 65 70 75

<210> 1138
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 1138
 Gly Glu Val Gly Asp Ser Asp Arg Gln Pro Trp Leu Gln Leu His His
 1 5 10 15
 Leu Cys Leu Pro Ser Leu Ala Arg Leu Phe Glu Gly Met Gln Glu Ala
 20 25 30
 Gly His

<210> 1139
 <211> 86
 <212> PRT
 <213> Homo sapiens

<400> 1139
 Gly Ser Gly Gly Leu Ser Gly Arg Leu Cys Leu Gly Met Val Ser Gln
 1 5 10 15
 Arg Ala Ser Trp Cys His Gln Trp Asp Glu Leu Leu Trp Cys Ser Cys
 20 25 30
 Val Ser Leu Asp Leu Ser Leu Glu Ala His Pro Phe Leu Pro Val Ala
 35 40 45
 Gly Ser Gly Ser Gly Val Val Val Phe His Gln Gln Ala Arg Leu Gly
 50 55 60
 Leu Glu Arg Trp Ala Gly Val Leu Cys Arg Leu His Leu Gly Leu Val
 65 70 75 80
 Ser Gly Pro Glu Cys Pro
 85

<210> 1140
 <211> 41
 <212> PRT
 <213> Homo sapiens

<400> 1140
 Gln Trp Asp Glu Leu Leu Trp Cys Ser Cys Val Ser Leu Asp Leu Ser
 1 5 10 15

572

Leu Glu Ala His Pro Phe Leu Pro Val Ala Gly Ser Gly Ser Gly Val
 20 25 30

Val Val Phe His Gln Gln Ala Arg Leu
 35 40

<210> 1141

<211> 247

<212> PRT

<213> Homo sapiens

<400> 1141

Met Arg Pro Asp Trp Lys Ala Gly Ala Gly Pro Gly Gly Pro Pro Gln
 1 5 10 15

Lys Pro Ala Pro Ser Ser Gln Arg Lys Pro Pro Ala Arg Pro Ser Ala
 20 25 30

Ala Ala Ala Ala Ile Ala Val Ala Ala Ala Glu Glu Glu Arg Arg Leu
 35 40 45

Arg Gln Arg Asn Arg Leu Arg Leu Glu Glu Asp Lys Pro Ala Val Glu
 50 55 60

Arg Cys Leu Glu Glu Leu Val Phe Gly Asp Val Glu Asn Asp Glu Asp
 65 70 75 80

Ala Leu Leu Arg Arg Leu Arg Gly Pro Arg Val Gln Glu His Glu Asp
 85 90 95

Ser Gly Asp Ser Glu Val Glu Asn Glu Ala Lys Gly Asn Phe Pro Pro
 100 105 110

Gln Lys Lys Pro Val Trp Val Asp Glu Glu Asp Glu Asp Glu Glu Met
 115 120 125

Val Asp Met Met Asn Asn Arg Phe Arg Lys Asp Met Met Lys Asn Ala
 130 135 140

Ser Glu Ser Lys Leu Ser Lys Asp Asn Leu Lys Lys Arg Leu Lys Glu
 145 150 155 160

Glu Phe Gln His Ala Met Gly Gly Val Pro Ala Trp Ala Glu Thr Thr
 165 170 175

Lys Arg Lys Thr Ser Ser Asp Asp Glu Ser Glu Glu Asp Glu Asp Asp
 180 185 190

Leu Leu Gln Arg Thr Gly Asn Phe Ile Ser Thr Ser Thr Ser Leu Pro
 195 200 205

Arg Gly Ile Leu Lys Met Lys Asn Cys Gln His Ala Asn Ala Glu Arg
 210 215 220

Pro Thr Val Ala Arg Ile Ser Ile Cys Ala Val Pro Ser Arg Cys Thr
 225 230 235 240

573

Asp Cys Asp Gly Cys Trp Asp
245

<210> 1142

<211> 180

<212> PRT

<213> Homo sapiens

<400> 1142

Cys Leu Glu Glu Leu Val Phe Gly Asp Val Glu Asn Asp Glu Asp Ala
1 5 10 15

Leu Leu Arg Arg Leu Arg Gly Pro Arg Val Gln Glu His Glu Asp Ser
20 25 30

Gly Asp Ser Glu Val Glu Asn Glu Ala Lys Gly Asn Phe Pro Pro Gln
35 40 45

Lys Lys Pro Val Trp Val Asp Glu Glu Asp Glu Asp Glu Glu Met Val
50 55 60

Asp Met Met Asn Asn Arg Phe Arg Lys Asp Met Met Lys Asn Ala Ser
65 70 75 80

Glu Ser Lys Leu Ser Lys Asp Asn Leu Lys Lys Arg Leu Lys Glu Glu
85 90 95

Phe Gln His Ala Met Gly Gly Val Pro Ala Trp Ala Glu Thr Thr Lys
100 105 110

Arg Lys Thr Ser Ser Asp Asp Glu Ser Glu Glu Asp Glu Asp Asp Leu
115 120 125

Leu Gln Arg Thr Gly Asn Phe Ile Ser Thr Ser Thr Ser Leu Pro Arg
130 135 140

Gly Ile Leu Lys Met Lys Asn Cys Gln His Ala Asn Ala Glu Arg Pro
145 150 155 160

Thr Val Ala Arg Ile Ser Ile Cys Ala Val Pro Ser Arg Cys Thr Asp
165 170 175

Cys Asp Gly Cys
180

<210> 1143

<211> 218

<212> PRT

<213> Homo sapiens

<400> 1143

Leu Lys Glu Lys Ile Val Arg Ser Phe Glu Val Ser Pro Asp Gly Ser
1 5 10 15

Phe Leu Leu Ile Asn Gly Ile Ala Gly Tyr Leu His Leu Leu Ala Met

574

20	25	30
Lys Thr Lys Glu Leu Ile Gly Ser Met Lys Ile Asn Gly Arg Val Ala		
35	40	45
Ala Ser Thr Phe Ser Ser Asp Ser Lys Lys Val Tyr Ala Ser Ser Gly		
50	55	60
Asp Gly Glu Val Tyr Val Trp Asp Val Asn Ser Arg Lys Cys Leu Asn		
65	70	75
Arg Phe Val Asp Glu Gly Ser Leu Tyr Gly Leu Ser Ile Ala Thr Ser		
85	90	95
Arg Asn Gly Gln Tyr Val Ala Cys Gly Ser Asn Cys Gly Val Val Asn		
100	105	110
Ile Tyr Asn Gln Asp Ser Cys Leu Gln Glu Thr Asn Pro Lys Pro Ile		
115	120	125
Lys Ala Ile Met Asn Leu Val Thr Gly Val Thr Ser Leu Thr Phe Asn		
130	135	140
Pro Thr Thr Glu Ile Leu Ala Ile Ala Ser Glu Lys Met Lys Glu Ala		
145	150	155
Val Arg Leu Val His Leu Pro Ser Cys Thr Val Phe Ser Asn Phe Pro		
165	170	175
Val Ile Lys Asn Lys Asn Ile Ser His Val His Thr Met Asp Phe Ser		
180	185	190
Pro Arg Ser Gly Tyr Phe Ala Leu Gly Asn Glu Lys Gly Lys Ala Leu		
195	200	205
Met Tyr Arg Leu His His Tyr Ser Asp Phe		
210	215	

<210> 1144

<211> 167

<212> PRT

<213> Homo sapiens

<400> 1144

Lys Ile Asn Gly Arg Val Ala Ala Ser Thr Phe Ser Ser Asp Ser Lys		
1	5	10
Lys Val Tyr Ala Ser Ser Gly Asp Gly Glu Val Tyr Val Trp Asp Val		
20	25	30
Asn Ser Arg Lys Cys Leu Asn Arg Phe Val Asp Glu Gly Ser Leu Tyr		
35	40	45
Gly Leu Ser Ile Ala Thr Ser Arg Asn Gly Gln Tyr Val Ala Cys Gly		
50	55	60
Ser Asn Cys Gly Val Val Asn Ile Tyr Asn Gln Asp Ser Cys Leu Gln		

[illegible]

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<400> 1145
Trp Leu Leu Gly Leu Asp Asn Ala Val Ser Leu Phe Gln Val Asp Gly
  1             5             10             15
Lys Thr Asn Pro Lys Ile Gln Ser Ile Tyr Leu Glu Arg Phe Pro Ile
      20             25             30
Phe Lys Ala Cys Phe Ser Ala Asn Gly Glu Glu Val Leu Ala Thr Ser
      35             40             45
Thr His Ser Lys Val Leu Tyr Val Tyr Asp
      50             55

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<400> 1146
Leu Val Phe Gly Asp Val Glu Asn Asp Glu Asp Ala Leu Leu Arg Arg
 1             5             10             15
Leu Arg Gly Pro Arg Val Gln
          20

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<210> 1147
<211> 29
<212> PRT
<213> Homo sapiens
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576

<400> 1147

Lys Asn Ala Ser Glu Ser Lys Leu Ser Lys Asp Asn Leu Lys Lys Arg
 1 5 10 15

Leu Lys Glu Glu Phe Gln His Ala Met Gly Gly Val Pro
 20 25

<210> 1148

<211> 23

<212> PRT

<213> Homo sapiens

<400> 1148

Ser Leu Pro Arg Gly Ile Leu Lys Met Lys Asn Cys Gln His Ala Asn
 1 5 10 15

Ala Glu Arg Pro Thr Val Ala
 20

<210> 1149

<211> 246

<212> PRT

<213> Homo sapiens

<400> 1149

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val
 1 5 10 15

Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Leu His Ser
 20 25 30

Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly
 35 40 45

Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu
 50 55 60

Lys Pro Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu
 65 70 75 80

Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro
 85 90 95

Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met
 100 105 110

Leu Val Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro
 115 120 125

Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Ser Phe
 130 135 140

Pro Ala Gly Ala Ala Arg Pro Asp Pro Ser Tyr Ala Cys Leu Thr Pro
 145 150 155 160

Cys Asp Ala Pro Thr Ser Pro Ser Leu Ser Thr Arg Ser Val Arg Thr

577

165 170 175
 Pro Thr Pro Ala Thr Ser Gln Thr Pro Trp Cys Val Pro Ala Cys Arg
 180 185 190
 Lys Gly Ala Arg Thr Pro Ala Arg Val Thr Pro Gly Ala Leu Trp Ser
 195 200 205
 Val Thr Ser Leu Phe Lys Ala Leu Ser Pro Gly Ala Arg Ile Arg Val
 210 215 220
 Arg Ser Pro Glu Ser Leu Val Ser Thr Arg Lys Ser Ala Asn Met Trp
 225 230 235 240
 Thr Gly Ser Arg Arg Arg
 245

<210> 1150

<211> 228

<212> PRT

<213> Homo sapiens

<400> 1150

Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Leu His Ser Gln Pro
 1 5 10 15
 Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly Ala Thr
 20 25 30
 Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu Lys Pro
 35 40 45
 Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu Glu Gly
 50 55 60
 Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro Gly Phe
 65 70 75 80
 Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met Leu Val
 85 90 95
 Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro Leu Thr
 100 105 110
 Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Ser Phe Pro Ala
 115 120 125
 Gly Ala Ala Arg Pro Asp Pro Ser Tyr Ala Cys Leu Thr Pro Cys Asp
 130 135 140
 Ala Pro Thr Ser Pro Ser Leu Ser Thr Arg Ser Val Arg Thr Pro Thr
 145 150 155 160
 Pro Ala Thr Ser Gln Thr Pro Trp Cys Val Pro Ala Cys Arg Lys Gly
 165 170 175
 Ala Arg Thr Pro Ala Arg Val Thr Pro Gly Ala Leu Trp Ser Val Thr

578

180 185 190

Ser Leu Phe Lys Ala Leu Ser Pro Gly Ala Arg Ile Arg Val Arg Ser
195 200 205

Pro Glu Ser Leu Val Ser Thr Arg Lys Ser Ala Asn Met Trp Thr Gly
210 215 220

Ser Arg Arg Arg
225

<210> 1151
 <211> 74
 <212> PRT
 <213> Homo sapiens

<400> 1151

Cys Lys Leu His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr
1 5 10 15

Arg Leu Leu Cys Gly Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr
20 25 30

Ala Ala His Cys Leu Lys Pro Arg Tyr Ile Val His Leu Gly Gln His
35 40 45

Asn Leu Gln Lys Glu Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu
50 55 60

Ser Phe Pro His Pro Gly Phe Asn Asn Ser
65 70

<210> 1152
 <211> 81
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (21)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (22)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1152

Val Leu Gln Gly Arg Tyr Phe Ser Pro Ile Leu Glu Met Arg Arg Leu
1 5 10 15

Arg Pro Glu Gly Xaa Xaa Asn Leu Pro Gly Gly Ser Arg Ala Gln Lys
20 25 30

Glu Pro Arg Gln Asp Leu Thr Leu Val Leu Trp Pro His Cys Pro His
35 40 45

579

Phe Ala Met Thr Arg Ser Tyr Val Pro Thr Lys Gln Cys Met Val Gln
 50 55 60

Gly Ser Phe Tyr Cys Ile Phe Ile Phe Lys Gly Pro Val Gln Asn Trp
 65 70 75 80

Cys

<210> 1153

<211> 24

<212> PRT

<213> Homo sapiens

<400> 1153

Cys Pro Arg Arg Arg Thr Cys Val Arg Val Glu Lys Ser Arg Pro Phe
 1 5 10 15

Gln Cys Gln Leu His Ser Ile Ser
 20

<210> 1154

<211> 8

<212> PRT

<213> Homo sapiens

<400> 1154

Pro Lys Glu Pro Gly Val Pro Glu
 1 5

<210> 1155

<211> 104

<212> PRT

<213> Homo sapiens

<400> 1155

Leu Gln Leu Lys Pro Arg Asp Pro Phe Ser Thr Leu Gly Pro Asn Ala
 1 5 10 15

Val Leu Ser Pro Gln Arg Leu Val Leu Glu Thr Leu Ser Lys Leu Ser
 20 25 30

Ile Gln Asp Asn Asn Val Asp Leu Ile Leu Ala Thr Pro Pro Phe Ser
 35 40 45

Arg Leu Glu Lys Leu Tyr Ser Thr Met Val Arg Phe Leu Ser Asp Arg
 50 55 60

Lys Asn Pro Val Cys Arg Arg Trp Leu Trp Tyr Cys Trp Pro Thr Trp
 65 70 75 80

Leu Arg Gly Thr Ala Trp Gln Leu Val Pro Leu Gln Cys Arg Arg Ala
 85 90 95

580

Val Ser Ala Thr Ser Trp Ala Ser
100

<210> 1156
<211> 27
<212> PRT
<213> Homo sapiens

<400> 1156
Arg Asp Pro Phe Ser Thr Leu Gly Pro Asn Ala Val Leu Ser Pro Gln
1 5 10 15

Arg Leu Val Leu Glu Thr Leu Ser Lys Leu Ser
20 25

<210> 1157
<211> 105
<212> PRT
<213> Homo sapiens

<400> 1157
Glu Val Ile Ser Gly Leu Phe Ile Gln Ser Arg Arg Arg Glu Arg Gly
1 5 10 15

Gln Gly Val Val Gly Ser His Met Ile Leu Trp Gly Lys Ser Leu Phe
20 25 30

Phe Phe Ser Pro Gln Arg Leu Thr Lys Asn Ile Phe Lys Asn Tyr Ser
35 40 45

Leu Leu Leu Thr Gln Arg Phe Leu Phe Pro Cys Glu Thr Leu Leu Leu
50 55 60

Gln Tyr Val Tyr Ser Ile Arg Cys Thr Val Gln Tyr Met Lys Gly Ser
65 70 75 80

Thr Leu Tyr Cys Thr Gly Leu Ser Ser Glu Gln Gly Leu Phe Thr Thr
85 90 95

Ala Asn Phe Leu Ala Pro Ala Arg Leu
100 105

<210> 1158
<211> 23
<212> PRT
<213> Homo sapiens

<400> 1158
Ile Arg Cys Thr Val Gln Tyr Met Lys Gly Ser Thr Leu Tyr Cys Thr
1 5 10 15

Gly Leu Ser Ser Glu Gln Gly
20

581

<210> 1159

<211> 211

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (103)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (153)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1159

Met	Pro	Ile	Ile	Asp	Gln	Val	Asn	Pro	Glu	Leu	His	Asp	Phe	Met	Gln
1				5					10					15	

Ser	Ala	Glu	Val	Gly	Thr	Ile	Phe	Ala	Leu	Ser	Trp	Leu	Ile	Thr	Trp
		20					25						30		

Phe	Gly	His	Val	Leu	Ser	Asp	Phe	Arg	His	Val	Val	Arg	Leu	Tyr	Asp
	35						40					45			

Phe	Phe	Leu	Ala	Cys	His	Pro	Leu	Met	Pro	Ile	Tyr	Phe	Ala	Ala	Val
	50				55						60				

Ile	Val	Leu	Tyr	Arg	Glu	Gln	Glu	Val	Leu	Asp	Cys	Asp	Cys	Asp	Met
65				70						75					80

Ala	Ser	Val	His	His	Leu	Leu	Ser	Gln	Ile	Pro	Gln	Asp	Leu	Pro	Tyr
			85						90						95

Glu	Thr	Leu	Ile	Ser	Arg	Xaa	Glu	Thr	Phe	Leu	Phe	Ser	Phe	Pro	His
		100						105					110		

Pro	Asn	Leu	Leu	Gly	Arg	Pro	Leu	Pro	Asn	Ser	Lys	Leu	Arg	Gly	Arg
	115						120						125		

Gln	Pro	Leu	Leu	Ser	Lys	Thr	Leu	Ser	Trp	His	Gln	Pro	Ser	Arg	Gly
	130					135					140				

Leu	Ile	Trp	Cys	Cys	Gly	Ser	Gly	Xaa	Arg	Gly	Leu	Leu	Arg	Pro	Glu
145					150					155					160

Asp	Arg	Thr	Lys	Asp	Val	Leu	Thr	Lys	Pro	Arg	Thr	Asn	Arg	Phe	Val
			165						170					175	

Lys	Leu	Ala	Val	Met	Gly	Leu	Thr	Val	Ala	Leu	Gly	Ala	Ala	Ala	Leu
		180						185					190		

Ala	Val	Val	Lys	Ser	Ala	Leu	Glu	Trp	Ala	Pro	Lys	Phe	Gln	Leu	Gln
		195					200						205		

Leu	Phe	Pro
		210

582

<210> 1160
 <211> 70
 <212> PRT
 <213> Homo sapiens

<400> 1160
 Cys Pro Glu Phe Phe Ile Pro Ala Thr Leu Pro Cys Pro Phe Val Phe
 1 5 10 15
 Ala Phe Thr Ser Glu Ala Ser Ser Arg Ala Tyr Leu Thr Gln Arg Gly
 20 25 30
 Pro Gly Gly Leu Ala Gln Asn Leu Met Pro Leu Pro Val Gly Phe Trp
 35 40 45
 Met Gly Ser Leu Pro Pro Pro Trp Cys Trp Arg Lys Trp Val Ser Glu
 50 55 60
 Ala Cys Ser Cys Phe Cys
 65 70

<210> 1161
 <211> 85
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (22)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1161
 Cys Arg Gln Ala Gly Ala Val Arg Gly His Pro Met Phe Gln Phe Thr
 1 5 10 15
 Phe Tyr Gly Val Thr Xaa Arg Phe Pro Val Thr Arg Ala Ala Gln Ala
 20 25 30
 Gln Gln Val Ala Lys Ala Ala Ala Ser Phe Arg Asn Pro Leu Pro Pro
 35 40 45
 Thr Pro Gly Arg Trp Gln Arg Ala His Pro Lys Ala His Trp Glu Arg
 50 55 60
 His Lys Ile Leu Cys Gln Ala Pro Arg Ser Pro Leu Cys Gln Val Gly
 65 70 75 80
 Ser Ala Thr Gly Leu
 85

<210> 1162
 <211> 217
 <212> PRT
 <213> Homo sapiens

583

<220>

<221> SITE

<222> (109)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (159)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1162

His Ile Leu Asn Tyr Leu Met Pro Ile Ile Asp Gln Val Asn Pro Glu
 1 5 10 15

Leu His Asp Phe Met Gln Ser Ala Glu Val Gly Thr Ile Phe Ala Leu
 20 25 30

Ser Trp Leu Ile Thr Trp Phe Gly His Val Leu Ser Asp Phe Arg His
 35 40 45

Val Val Arg Leu Tyr Asp Phe Phe Leu Ala Cys His Pro Leu Met Pro
 50 55 60

Ile Tyr Phe Ala Ala Val Ile Val Leu Tyr Arg Glu Gln Glu Val Leu
 65 70 75 80

Asp Cys Asp Cys Asp Met Ala Ser Val His His Leu Leu Ser Gln Ile
 85 90 95

Pro Gln Asp Leu Pro Tyr Glu Thr Leu Ile Ser Arg Xaa Glu Thr Phe
 100 105 110

Leu Phe Ser Phe Pro His Pro Asn Leu Leu Gly Arg Pro Leu Pro Asn
 115 120 125

Ser Lys Leu Arg Gly Arg Gln Pro Leu Leu Ser Lys Thr Leu Ser Trp
 130 135 140

His Gln Pro Ser Arg Gly Leu Ile Trp Cys Cys Gly Ser Gly Xaa Arg
 145 150 155 160

Gly Leu Leu Arg Pro Glu Asp Arg Thr Lys Asp Val Leu Thr Lys Pro
 165 170 175

Arg Thr Asn Arg Phe Val Lys Leu Ala Val Met Gly Leu Thr Val Ala
 180 185 190

Leu Gly Ala Ala Ala Leu Ala Val Val Lys Ser Ala Leu Glu Trp Ala
 195 200 205

Pro Lys Phe Gln Leu Gln Leu Phe Pro
 210 215

<210> 1163

<211> 31

<212> PRT

<213> Homo sapiens

584

<400> 1163

Ala Glu Val Gly Thr Ile Phe Ala Leu Ser Trp Leu Ile Thr Trp Phe
1 5 10 15

Gly His Val Leu Ser Asp Phe Arg His Val Val Arg Leu Tyr Asp
20 25 30

<210> 1164

<211> 33

<212> PRT

<213> Homo sapiens

<400> 1164

Val Leu Thr Lys Pro Arg Thr Asn Arg Phe Val Lys Leu Ala Val Met
1 5 10 15

Gly Leu Thr Val Ala Leu Gly Ala Ala Ala Leu Ala Val Val Lys Ser
20 25 30

Ala

<210> 1165

<211> 20

<212> PRT

<213> Homo sapiens

<400> 1165

Gly Phe Gly Ser Val Ser Ala Ala Gly Arg Arg Ser Gly Gly Thr Trp
1 5 10 15

Gln Pro Val Gln
20

<210> 1166

<211> 16

<212> PRT

<213> Homo sapiens

<400> 1166

Pro Gly Gly Leu Ala Val Gly Ser Arg Trp Trp Ser Arg Ser Leu Thr
1 5 10 15

<210> 1167

<211> 30

<212> PRT

<213> Homo sapiens

<400> 1167

Leu Glu Pro Ser Arg Gln Arg Arg Pro Arg Arg Arg Gly Gly Thr Ser

585

1 5 10 15
 Arg Pro Glu Thr Asp Gln Arg Ala Lys Cys Trp Arg Gln Leu
 20 25 30

<210> 1168
 <211> 11
 <212> PRT
 <213> Homo sapiens

<400> 1168
 Val Cys Leu Arg Cys Gln Asn Arg Met Glu Asn
 1 5 10

<210> 1169
 <211> 367
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (22)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (102)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1169
 Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val
 1 5 10 15
 Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala
 20 25 30
 Ala Xaa Ala Gly Ala Phe Ser Pro Ala Ser Thr Thr Thr Thr Arg Arg
 35 40 45
 His Leu Ser Ser Arg Asn Arg Pro Glu Gly Lys Val Leu Glu Thr Val
 50 55 60
 Gly Val Phe Glu Val Pro Lys Gln Asn Gly Lys Tyr Glu Thr Gly Gln
 65 70 75 80
 Leu Phe Leu His Ser Ile Phe Gly Tyr Arg Gly Val Val Leu Phe Pro
 85 90 95
 Trp Gln Ala Arg Leu Xaa Asp Arg Asp Val Ala Ser Ala Ala Pro Glu
 100 105 110

586

Lys Ala Glu Asn Pro Ala Gly His Gly Ser Lys Glu Val Lys Gly Lys
 115 120 125
 Thr His Thr Tyr Tyr Gln Val Leu Ile Asp Ala Arg Asp Cys Pro His
 130 135 140
 Ile Ser Gln Arg Ser Gln Thr Glu Ala Val Thr Phe Leu Ala Asn His
 145 150 155 160
 Asp Asp Ser Arg Ala Leu Tyr Ala Ile Pro Gly Leu Asp Tyr Val Ser
 165 170 175
 His Glu Asp Ile Leu Pro Tyr Thr Ser Thr Asp Gln Val Pro Ile Gln
 180 185 190
 His Glu Leu Phe Glu Arg Phe Leu Leu Tyr Asp Gln Thr Lys Ala Pro
 195 200 205
 Pro Phe Val Ala Arg Glu Thr Leu Arg Ala Trp Gln Glu Lys Asn His
 210 215 220
 Pro Trp Leu Glu Leu Ser Asp Val His Arg Glu Thr Thr Glu Asn Ile
 225 230 235 240
 Arg Val Thr Val Ile Pro Phe Tyr Met Gly Met Arg Glu Ala Gln Asn
 245 250 255
 Ser His Val Tyr Trp Trp Arg Tyr Cys Ile Arg Leu Glu Asn Leu Asp
 260 265 270
 Ser Asp Val Val Gln Leu Arg Glu Arg His Trp Arg Ile Phe Ser Leu
 275 280 285
 Ser Gly Thr Leu Glu Thr Val Arg Gly Arg Gly Val Val Gly Arg Glu
 290 295 300
 Pro Val Leu Ser Lys Glu Gln Pro Ala Phe Gln Tyr Ser Ser His Val
 305 310 315 320
 Ser Leu Gln Ala Ser Ser Gly His Met Trp Gly Thr Phe Arg Phe Glu
 325 330 335
 Arg Pro Asp Gly Ser His Phe Asp Val Arg Ile Pro Pro Phe Ser Leu
 340 345 350
 Glu Ser Asn Lys Asp Glu Lys Thr Pro Pro Ser Gly Leu His Trp
 355 360 365

<210> 1170

<211> 33

<212> PRT

<213> Homo sapiens

<220> .

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

587

<400> 1170

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala
20 25 30

Ala

<210> 1171

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1171

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala
20 25 30

Ala

<210> 1172

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1172

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala
20 25 30

Ala

<210> 1173

<211> 33

<212> PRT

<213> Homo sapiens

588

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1173

Met	Ala	Ala	Cys	Thr	Ala	Arg	Arg	Pro	Gly	Arg	Gly	Gln	Pro	Leu	Val
1				5					10					15	

Val	Pro	Val	Ala	Asp	Xaa	Gly	Pro	Val	Ala	Lys	Ala	Ala	Leu	Cys	Ala
			20					25						30	

Ala

<210> 1174

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1174

Met	Ala	Ala	Cys	Thr	Ala	Arg	Arg	Pro	Gly	Arg	Gly	Gln	Pro	Leu	Val
1				5					10					15	

Val	Pro	Val	Ala	Asp	Xaa	Gly	Pro	Val	Ala	Lys	Ala	Ala	Leu	Cys	Ala
			20					25						30	

Ala

<210> 1175

<211> 35

<212> PRT

<213> Homo sapiens

<400> 1175

Val	Leu	Glu	Thr	Val	Gly	Val	Phe	Glu	Val	Pro	Lys	Gln	Asn	Gly	Lys
1				5						10				15	

Tyr	Glu	Thr	Gly	Gln	Leu	Phe	Leu	His	Ser	Ile	Phe	Gly	Tyr	Arg	Gly
			20					25					30		

Val	Val	Leu
		35

<210> 1176

<211> 16

<212> PRT

<213> Homo sapiens

589

<400> 1176

Gly Leu Asp Tyr Val Ser His Glu Asp Ile Leu Pro Tyr Thr Ser Thr
1 5 10 15

<210> 1177

<211> 19

<212> PRT

<213> Homo sapiens

<400> 1177

Asp Val His Arg Glu Thr Thr Glu Asn Ile Arg Val Thr Val Ile Pro
1 5 10 15

Phe Tyr Met

<210> 1178

<211> 21

<212> PRT

<213> Homo sapiens

<400> 1178

Trp Trp Arg Tyr Cys Ile Arg Leu Glu Asn Leu Asp Ser Asp Val Val
1 5 10 15

Gln Leu Arg Glu Arg
20

<210> 1179

<211> 26

<212> PRT

<213> Homo sapiens

<400> 1179

Pro Ala Phe Gln Tyr Ser Ser His Val Ser Leu Gln Ala Ser Ser Gly
1 5 10 15

His Met Trp Gly Thr Phe Arg Phe Glu Arg
20 25

<210> 1180

<211> 230

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (114)

<223> Xaa equals any of the naturally occurring L-amino acids

590

<220>

<221> SITE

<222> (182)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (194)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1180

Arg Leu Pro Ser His Lys Arg Arg Cys Phe Cys Leu Val Ile Gln Lys
 1 5 10 15

Lys Ser Phe Lys Glu Phe Met Leu Asp Gly Asn Leu Ile Ser Gly Gly
 20 25 30

Val Gly Glu Asp Val Phe Met Ala Asp Ile Val Gln Ala Trp Asp Gly
 35 40 45

Ile Glu Gly Pro Thr Val Ile Met Val Ser Gln Glu Gly His Ser Phe
 50 55 60

Cys Leu Arg Ser Leu Arg Tyr Met Trp Ala Val Thr Ser Ile Asn Gln
 65 70 75 80

His Leu Ile Val Ser Val Ser Phe Ala Phe His Leu Leu Gly Ala Met
 85 90 95

Ala Ser Arg Val Leu Cys Phe Phe Trp Ser Cys Arg Ser His Ile Pro
 100 105 110

Val Xaa Gln Ser Gly Leu Pro Gly Lys Gln Asp Asp Thr Ser Val Ala
 115 120 125

Lys Asn Ala Met Lys Glu Lys Leu Pro Gly Leu Ile Phe Ser Ile Leu
 130 135 140

Phe Trp His Leu Lys His Thr Asn Cys Leu Gln His Phe Ala Leu Trp
 145 150 155 160

Ser Val Ser Gly Arg Glu Val Pro Pro Arg Arg Arg Gly Arg Arg Trp
 165 170 175

Arg Glu Gly Ser Ser Xaa Gly Arg Ala Gln Ser Gly Leu Gly His Arg
 180 185 190

Ala Xaa Val Ser Asp Arg Asp His Gln Arg Leu Pro Thr Ala Arg Pro
 195 200 205

Pro Gly Cys Thr Gly Cys His Val Pro Pro Glu Arg Arg Pro Ala Ala
 210 215 220

Asp Thr Glu Pro Asn Pro
 225 230

<210> 1181

591

<211> 31
<212> PRT
<213> Homo sapiens

<400> 1181
Lys Glu Phe Met Leu Asp Gly Asn Leu Ile Ser Gly Gly Val Gly Glu
1 5 10 15
Asp Val Phe Met Ala Asp Ile Val Gln Ala Trp Asp Gly Ile Glu
20 25 30

<210> 1182
<211> 29
<212> PRT
<213> Homo sapiens

<400> 1182
Ala Val Thr Ser Ile Asn Gln His Leu Ile Val Ser Val Ser Phe Ala
1 5 10 15
Phe His Leu Leu Gly Ala Met Ala Ser Arg Val Leu Cys
20 25

<210> 1183
<211> 20
<212> PRT
<213> Homo sapiens

<400> 1183
Thr Ala Arg Pro Pro Gly Cys Thr Gly Cys His Val Pro Pro Glu Arg
1 5 10 15
Arg Pro Ala Ala
20

<210> 1184
<211> 11
<212> PRT
<213> Homo sapiens

<400> 1184
Ser Leu Cys Cys Pro Glu Gly Ala Glu Gly Cys
1 5 10

<210> 1185
<211> 12
<212> PRT
<213> Homo sapiens

<400> 1185
Gln Leu Lys Lys Thr His Tyr Asp Arg Pro Cys Pro
1 5 10

592

<210> 1186
 <211> 12
 <212> PRT
 <213> Homo sapiens

<400> 1186
 Gln Leu Lys Lys Thr His Tyr Asp Arg Pro Cys Pro
 1 5 10

<210> 1187
 <211> 29
 <212> PRT
 <213> Homo sapiens

<400> 1187
 Met Asn Arg Pro Cys Pro Phe Cys Leu Trp Lys Val Phe Pro Leu Leu
 1 5 10 15

Leu Leu Leu His Glu Glu Leu Phe Pro Leu Pro Val Pro
 20 25

<210> 1188
 <211> 33
 <212> PRT
 <213> Homo sapiens

<400> 1188
 Lys Glu Lys Thr Phe Thr Pro Arg Asn Ser Leu Cys Cys Pro Glu Gly
 1 5 10 15

Ala Glu Gly Cys Ile Ala Gly Gly Asp Leu Gln Leu Lys Lys Thr His
 20 25 30

Tyr

<210> 1189
 <211> 170
 <212> PRT
 <213> Homo sapiens

<400> 1189
 Ala Gln Arg Lys Lys Glu Met Val Leu Ser Glu Lys Val Ser Gln Leu
 1 5 10 15

Met Glu Trp Thr Asn Lys Arg Pro Val Ile Arg Met Asn Gly Asp Lys
 20 25 30

Phe Arg Arg Leu Val Lys Ala Pro Pro Arg Asn Tyr Ser Val Ile Val
 35 40 45

Met Phe Thr Ala Leu Gln Leu His Arg Gln Cys Val Val Cys Lys Gln
 50 55 60

Ala Asp Glu Glu Phe Gln Ile Leu Ala Asn Ser Trp Arg Tyr Ser Ser

593

65		70		75		80
Ala Phe Thr Asn Arg Ile Phe Phe Ala Met Val Asp Phe Asp Glu Gly	85		90		95	
Ser Asp Val Phe Gln Met Leu Asn Met Asn Ser Ala Pro Thr Phe Ile	100		105		110	
Asn Phe Pro Ala Lys Gly Lys Pro Lys Arg Gly Asp Thr Tyr Glu Leu	115		120		125	
Gln Val Arg Gly Phe Ser Ala Glu Gln Ile Ala Arg Trp Ile Ala Asp	130		135		140	
Arg Thr Asp Val Asn Ile Arg Val Ile Arg Pro Pro Asn Met Ala Ala	145		150		155	160
Arg Trp Arg Phe Trp Cys Val Ser Val Thr	165		170			

<210> 1190
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 1190
 Met Val Val Ala Leu Leu Ile Val Cys Asp Val Pro Ser Ala Ser
 1 5 10 15

<210> 1191
 <211> 16
 <212> PRT
 <213> Homo sapiens

<400> 1191
 Ala Gln Arg Lys Lys Glu Met Val Leu Ser Glu Lys Val Ser Gln Leu
 1 5 10 15

<210> 1192
 <211> 17
 <212> PRT
 <213> Homo sapiens

<400> 1192
 Met Glu Trp Thr Asn Lys Arg Pro Val Ile Arg Met Asn Gly Asp Lys
 1 5 10 15

Phe

<210> 1193

594

<211> 56

<212> PRT

<213> Homo sapiens

<400> 1193

Arg Arg Leu Val Lys Ala Pro Pro Arg Asn Tyr Ser Val Ile Val Met
 1 5 10 15

Phe Thr Ala Leu Gln Leu His Arg Gln Cys Val Val Cys Lys Gln Ala
 20 25 30

Asp Glu Glu Phe Gln Ile Leu Ala Asn Ser Trp Arg Tyr Ser Ser Ala
 35 40 45

Phe Thr Asn Arg Ile Phe Phe Ala
 50 55

<210> 1194

<211> 31

<212> PRT

<213> Homo sapiens

<400> 1194

Met Val Asp Phe Asp Glu Gly Ser Asp Val Phe Gln Met Leu Asn Met
 1 5 10 15

Asn Ser Ala Pro Thr Phe Ile Asn Phe Pro Ala Lys Gly Lys Pro
 20 25 30

<210> 1195

<211> 37

<212> PRT

<213> Homo sapiens

<400> 1195

Lys Arg Gly Asp Thr Tyr Glu Leu Gln Val Arg Gly Phe Ser Ala Glu
 1 5 10 15

Gln Ile Ala Arg Trp Ile Ala Asp Arg Thr Asp Val Asn Ile Arg Val
 20 25 30

Ile Arg Pro Pro Asn
 35

<210> 1196

<211> 44

<212> PRT

<213> Homo sapiens

<400> 1196

Tyr Ala Gly Pro Leu Met Leu Gly Leu Leu Leu Ala Val Ile Gly Gly
 1 5 10 15

Leu Val Tyr Leu Arg Arg Val Ile Trp Asn Phe Ser Leu Ile Lys Leu
 20 25 30

Asp Gly Leu Leu Gln Leu Cys Val Leu Cys Leu Leu
35 40

<400> 1197
Asp Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp
1 5 10 15

<400> 1198
Cys Gln Glu Gly Ala Lys Asp Met Trp Asp Lys Leu Arg Lys Glu Ser
1 5 10 15

<400> 1199
Val Leu Leu Val Ser Leu Ser Ala Ala Leu Ala Thr Trp Leu Ser Phe
1 5 10 15

<400> 1200
Met Gly Leu Lys Leu Asn Gly Arg Tyr Ile Ser Leu Ile Leu Ala Val
1 5 10 15

Gln Ile Ala Tyr Leu Val Gln Ala Val Arg Ala Ala Gly Lys Cys Asp
20 25 30

Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp Ser
35 40 45

596

<210> 1201

<211> 90

<212> PRT

<213> Homo sapiens

<400> 1201

Pro Ala Ala Trp Asp Asp Lys Thr Asn Ile Lys Thr Val Cys Thr Tyr
 1 5 10 15
 Trp Glu Asp Phe His Ser Cys Thr Val Thr Ala Leu Thr Asp Cys Gln
 20 25 30
 Glu Gly Ala Lys Asp Met Trp Asp Lys Leu Arg Lys Glu Ser Lys Asn
 35 40 45
 Leu Asn Ile Gln Gly Ser Leu Phe Glu Leu Cys Gly Ser Gly Asn Gly
 50 55 60
 Ala Ala Gly Ser Leu Leu Pro Ala Phe Pro Val Leu Leu Val Ser Leu
 65 70 75 80
 Ser Ala Ala Leu Ala Thr Trp Leu Ser Phe
 85 90

<210> 1202

<211> 143

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (51)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (52)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (53)

597

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1202

Met	Gly	Leu	Lys	Leu	Asn	Gly	Arg	Tyr	Ile	Ser	Leu	Ile	Leu	Ala	Val
1				5					10					15	

Gln	Ile	Ala	Tyr	Leu	Val	Gln	Ala	Val	Arg	Ala	Ala	Gly	Lys	Cys	Asp
		20						25					30		

Ala	Val	Phe	Lys	Gly	Phe	Ser	Asp	Cys	Leu	Leu	Lys	Leu	Gly	Asp	Ser
		35					40					45			

Xaa	Xaa	Xaa	Xaa	Xaa	Pro	Ala	Ala	Trp	Asp	Asp	Lys	Thr	Asn	Ile	Lys
50						55					60				

Thr	Val	Cys	Thr	Tyr	Trp	Glu	Asp	Phe	His	Ser	Cys	Thr	Val	Thr	Ala
65					70					75					80

Leu	Thr	Asp	Cys	Gln	Glu	Gly	Ala	Lys	Asp	Met	Trp	Asp	Lys	Leu	Arg
				85					90					95	

Lys	Glu	Ser	Lys	Asn	Leu	Asn	Ile	Gln	Gly	Ser	Leu	Phe	Glu	Leu	Cys
			100					105					110		

Gly	Ser	Gly	Asn	Gly	Ala	Ala	Gly	Ser	Leu	Leu	Pro	Ala	Phe	Pro	Val
		115					120					125			

Leu	Leu	Val	Ser	Leu	Ser	Ala	Ala	Leu	Ala	Thr	Trp	Leu	Ser	Phe	
130						135					140				

<210> 1203

<211> 34

<212> PRT

<213> Homo sapiens

<400> 1203

Met	Asn	Ser	Ala	Ala	Gly	Phe	Ser	His	Leu	Asp	Arg	Arg	Glu	Arg	Val
1				5					10					15	

Leu	Lys	Leu	Gly	Glu	Ser	Phe	Glu	Lys	Gln	Pro	Arg	Cys	Ala	Ser	Thr
			20					25					30		

Leu Cys

<210> 1204

<211> 28

<212> PRT

<213> Homo sapiens

<400> 1204

Thr	Ile	Tyr	Pro	Thr	Glu	Glu	Glu	Leu	Gln	Ala	Val	Gln	Lys	Ile	Val
1				5				10					15		

Ser	Ile	Thr	Glu	Arg	Ala	Leu	Lys	Leu	Val	Ser	Asp				
			20					25							

598

<210> 1205
<211> 30
<212> PRT
<213> Homo sapiens

<400> 1205
Arg Ala Leu Lys Gly Val Leu Arg Val Gly Val Leu Ala Lys Gly Leu
1 5 10 15
Leu Leu Arg Gly Asp Arg Asn Val Asn Leu Val Leu Leu Cys
20 25 30

<210> 1206
<211> 39
<212> PRT
<213> Homo sapiens

<400> 1206
Ala Leu Ala Ala Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn
1 5 10 15
Gly Leu Gln Ser Cys Val Ile Ile Ile Arg Ile Leu Arg Asp Leu Cys
20 25 30

Gln Arg Val Pro Thr Trp Ser
35

<210> 1207
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1207
Gly Asp Ala Leu Arg Arg Val Phe Glu Cys Ile Ser Ser Gly Ile Ile
1 5 10 15

Leu

<210> 1208
<211> 16
<212> PRT
<213> Homo sapiens

<400> 1208
Leu Ala Phe Arg Gln Ile His Lys Val Leu Gly Met Asp Pro Leu Pro
1 5 10 15

<210> 1209

599

<211> 342

<212> PRT

<213> Homo sapiens

<400> 1209

Thr Ile Tyr Pro Thr Glu Glu Glu Leu Gln Ala Val Gln Lys Ile Val
 1 5 10 15
 Ser Ile Thr Glu Arg Ala Leu Lys Leu Val Ser Asp Ser Leu Ser Glu
 20 25 30
 His Glu Lys Asn Lys Asn Lys Glu Gly Asp Asp Lys Lys Glu Gly Gly
 35 40 45
 Lys Asp Arg Ala Leu Lys Gly Val Leu Arg Val Gly Val Leu Ala Lys
 50 55 60
 Gly Leu Leu Leu Arg Gly Asp Arg Asn Val Asn Leu Val Leu Leu Cys
 65 70 75 80
 Ser Glu Lys Pro Ser Lys Thr Leu Leu Ser Arg Ile Ala Glu Asn Leu
 85 90 95
 Pro Lys Gln Leu Ala Val Ile Ser Pro Glu Lys Tyr Asp Ile Lys Cys
 100 105 110
 Ala Val Ser Glu Ala Ala Ile Ile Leu Asn Ser Cys Val Glu Pro Lys
 115 120 125
 Met Gln Val Thr Ile Thr Leu Thr Ser Pro Ile Ile Arg Glu Glu Asn
 130 135 140
 Met Arg Glu Gly Asp Val Thr Ser Gly Met Val Lys Asp Pro Pro Asp
 145 150 155 160
 Val Leu Asp Arg Gln Lys Cys Leu Asp Ala Leu Ala Ala Leu Arg His
 165 170 175
 Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Gln Ser Cys Val Ile
 180 185 190
 Ile Ile Arg Ile Leu Arg Asp Leu Cys Gln Arg Val Pro Thr Trp Ser
 195 200 205
 Asp Phe Pro Ser Trp Ala Met Glu Leu Leu Val Glu Lys Ala Ile Ser
 210 215 220
 Ser Ala Ser Ser Pro Gln Ser Pro Gly Asp Ala Leu Arg Arg Val Phe
 225 230 235 240
 Glu Cys Ile Ser Ser Gly Ile Ile Leu Lys Gly Ser Pro Gly Leu Leu
 245 250 255
 Asp Pro Cys Glu Lys Asp Pro Phe Asp Thr Leu Ala Thr Met Thr Asp
 260 265 270
 Gln Gln Arg Glu Asp Ile Thr Ser Ser Ala Gln Phe Ala Leu Arg Leu
 275 280 285

600

Leu Ala Phe Arg Gln Ile His Lys Val Leu Gly Met Asp Pro Leu Pro
 290 295 300

Gln Met Ser Gln Arg Phe Asn Ile His Asn Asn Arg Lys Arg Arg Arg
 305 310 315 320

Asp Ser Asp Gly Val Asp Gly Phe Glu Ala Glu Gly Lys Lys Asp Lys
 325 330 335

Lys Asp Tyr Asp Asn Phe
 340

<210> 1210

<211> 12

<212> PRT

<213> Homo sapiens

<400> 1210

Met Glu Arg His Pro Lys Lys Lys Met Cys Ser Asp
 1 5 10

<210> 1211

<211> 31

<212> PRT

<213> Homo sapiens

<400> 1211

Gly Glu Asn Ser Ser Ser Asp Phe Phe Pro Leu Phe Leu Phe Tyr Phe
 1 5 10 15

Leu Val Ala Leu Ala Ser Pro Pro Ile Phe Val Ser Phe Ile Asn
 20 25 30

<210> 1212

<211> 24

<212> PRT

<213> Homo sapiens

<400> 1212

Met Gly Ser Gln His Ser Ala Ala Ala Arg Pro Ser Ser Cys Arg Arg
 1 5 10 15

Lys Gln Glu Asp Asp Arg Asp Gly
 20

<210> 1213

<211> 30

<212> PRT

<213> Homo sapiens

<400> 1213

Leu Leu Ala Glu Arg Glu Gln Glu Glu Ala Ile Ala Gln Phe Pro Tyr
 1 5 10 15

Val Glu Phe Thr Gly Arg Asp Ser Ile Thr Cys Leu Thr Cys
20 25 30

<400> 1214
Gln Gly Thr Gly Tyr Ile Pro Thr Glu Gln Val Asn Glu Leu Val Ala
1 5 10 15
Leu Ile Pro His Ser Asp Gln Arg Leu Arg Pro Gln Arg Thr Lys Gln
20 25 30

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<400> 1215
Ala Arg Leu Asn Val Gly Arg Glu Ser Leu Lys Arg Glu Met Leu Lys
  1                               10                               15

Ser Gln Gly Val Lys Val Ser Glu Ser Pro Met Gly Ala Arg His Ser
      20                               25                               30

Ser Trp Pro Glu Gly Ala Ala Phe Cys Lys Lys Val Gln Gly Ala Gln
      35                               40                               45

Met Gln Phe Pro Pro Arg Arg
      50                               55

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<400> 1216
Ala Arg Leu Asn Val Gly Arg Glu Ser Leu Lys Arg Glu Met Leu
  1             5             10            15
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<400> 1217
Leu Lys Ser Gln Gly Val Lys Val Ser Glu Ser Pro Met Gly Ala Arg
1 5 10 15

602

His Ser Ser Trp
20

<210> 1218
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1218
Ala Phe Cys Lys Lys Val Gln Gly Ala Gln Met Gln Phe Pro Pro Arg
1 5 10 15

Arg

<210> 1219
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1219
Ala Phe Cys Lys Lys Val Gln Gly Ala Gln Met Gln Phe Pro Pro Arg
1 5 10 15

Arg

<210> 1220
<211> 26
<212> PRT
<213> Homo sapiens

<400> 1220
Asn Phe Phe Phe Val Cys Leu Phe Lys Ser Ser Leu Arg Leu Val Asn
1 5 10 15

Ser Ser Tyr Thr Pro Ile Leu Cys Val Leu
20 25

<210> 1221
<211> 37
<212> PRT
<213> Homo sapiens

<400> 1221
Val Gln Val Leu Glu Gln Leu Thr Asn Asn Ala Val Ala Glu Ser Arg
1 5 10 15

Phe Asn Asp Ala Ala Tyr Tyr Tyr Trp Met Leu Ser Met Gln Cys Leu
20 25 30

Asp Ile Ala Gln Asp
35

603

<210> 1222
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 1222
 Pro Ala Gln Lys Asp Thr Met Leu Gly Lys Phe Tyr His Phe Gln Arg
 1 5 10 15
 Leu Ala Glu Leu Tyr His Gly Tyr His Ala Ile His Arg His Thr Glu
 20 25 30
 Asp Pro

<210> 1223
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 1223
 Leu Ala Lys Gln Ser Lys Ala Leu Gly Ala Tyr Arg Leu Ala Arg His
 1 5 10 15
 Ala Tyr Asp Lys Leu Arg Gly Leu Tyr Ile Pro
 20 25

<210> 1224
 <211> 36
 <212> PRT
 <213> Homo sapiens

<400> 1224
 Ala Arg Phe Gln Lys Ser Ile Glu Leu Gly Thr Leu Thr Ile Arg Ala
 1 5 10 15
 Lys Pro Phe His Asp Ser Glu Glu Leu Val Pro Leu Cys Tyr Arg Cys
 20 25 30
 Ser Thr Asn Asn
 35

<210> 1225
 <211> 73
 <212> PRT
 <213> Homo sapiens

<400> 1225
 Pro Leu Leu Asn Asn Leu Gly Asn Val Cys Ile Asn Cys Arg Gln Pro
 1 5 10 15
 Phe Ile Phe Ser Ala Ser Ser Tyr Asp Val Leu His Leu Val Glu Phe
 20 25 30

604

Tyr Leu Glu Glu Gly Ile Thr Asp Glu Glu Ala Ile Ser Leu Ile Asp
 35 40 45

Leu Glu Val Leu Arg Pro Lys Arg Asp Asp Arg Gln Leu Glu Ile Cys
 50 55 60

Lys Gln Gln Leu Pro Asp Ser Cys Gly
 65 70

<210> 1226

<211> 29

<212> PRT

<213> Homo sapiens

<400> 1226

Met Pro Tyr Ala Gln Trp Leu Ala Glu Asn Asp Arg Phe Glu Glu Ala
 1 5 10 15

Gln Lys Ala Phe His Lys Ala Gly Arg Gln Arg Glu Ala
 20 25

<210> 1227

<211> 36

<212> PRT

<213> Homo sapiens

<400> 1227

Phe Ser Val His Arg Pro Glu Thr Leu Phe Asn Ile Ser Arg Phe Leu
 1 5 10 15

Leu His Ser Leu Pro Lys Asp Thr Pro Ser Gly Ile Ser Lys Val Lys
 20 25 30

Ile Leu Phe Thr
 35

<210> 1228

<211> 1384

<212> DNA

<213> Homo sapiens

<400> 1228

ggcagcagcg ttttcgggcc gtgcgtttgt ggccgtccgg cctccctgac atgcagccct 60
 ctggaccccg aggttgacc ctactgtgac acacctacca tgcggacact cttcaacctc 120
 ctctggcttg ccctggcctg cagccctgtt cacactaccc tgtcaaagtc agatgccaaa 180
 aaagccgcct caaagacgct gctggagaag agtcagtttt cagataagcc ggtgcaagac 240
 cgggggtttg tggtgacgga cctcaaagct gagagtgtgg ttcttgagca tcgcagctac 300
 tgctcggcaa aggcccgga cagacacttt gctggggatg tactgggcta tgtcactcca 360

605

tggaacagcc atggctacga tgtcaccaag gtctttggga gcaagttcac acagatctca	420
cccgtctggc tgcagctgaa gagacgtggc cgtgagatgt ttgaggtcac gggcctccac	480
gacgtggacc aaggggtggat gcgagctgtc aggaagcatg ccaagggcct gcacatagt	540
cctcggctcc tgtttgagga ctggacttac gatgatttcc ggaacgtctt agacagt	600
gatgagatag aggagctgag caagaccgtg gtccaggtgg caaagaacca gcatttcgat	660
ggcttcgtgg tggaggtctg gaaccagctg ctaagccaga agcgcgtggg cctcatccac	720
atgctcacc accctggcga ggctctgcac caggcccggtc tgctggccct cctggctac	780
ccgcctgcca tcacccccgg gaccgaccag ctgggcatgt tcacgcacaa ggagtttgag	840
cagctggccc ccgtgctgga tggtttcagc ctcatgacct acgactactc tacagcgcat	900
cagcctggcc ctaatgcacc cctgtcctgg gtccgagcct gcgtccaggt cctggaccgc	960
aagtccaagt ggcgaagcaa aatcctcctg gggctcaact tctatggtac atccagacac	1020
tgaaggacca caggccccgg atggtgtggg acagccaggt ctgagagcac ttcttcgagt	1080
acaagaagag ccgcagtggtg aggcacgtcg tcttctaccc aaccctgaag tccttcgagg	1140
tgcggctgga gctggccccg gagctgggctg ttggggctctc tatctgggag ctgggcccag	1200
gcctggacta cttctacgac ctgctctagg tgggcattgc ggctccgcg gtggacgtgt	1260
tcttttctaa gccatggagt gagtgagcag gtgtgaaata caggcctcca ctccgaaaaa	1320
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa	1380
aaaa	1384

<210> 1229

<211> 1334

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1268)

<223> n equals a,t,g, or c

<400> 1229

gcgctggagc gttttccggc cgtgcgtttg tggccgtccg gcctccctga catgcagccc	60
tctggacccc gaggttggac cctactgtga cacacctacc atgcggacac tcttcaacct	120
cctctggctt gccctggcct gcagccctgt tcacctacc ctgtcaaagt cagatgccaa	180
aaaagccgcc tcaaagacgc tgctggagaa gagtcagttt tcagataagc cggtgcaaga	240
ccgggggttg gtggtgacgg acctcaaagc tgagagtgtg gttcttgagc atcgagcta	300

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ctgctcggca aaggccccggg acagacactt tgctggggat gtactgggct atgtcactcc      360
atggaacagc catggctacg atgtcaccaa ggtctttggg agcaagttca cacagatctc      420
acccgtctgg ctgcagctga agagacgtgg ccgtgagatg tttgaggtca cgggcctcca      480
cgacgtggac caagggtgga tgcgagctgt caggaagcat gccaaaggcc tgcacatagt      540
gcctcggctc ctgtttgagg actggactta cgatgatttc cggaacgtct tagacagtga      600
ggatgagata gaggagctga gcaagaccgt ggtccagggt gcaaagaacc agcatttcga      660
tggettctgt gtggagggtct ggaaccagct gctaagccag aagcgcgtga ccgaccagct      720
gggcatgttc acgcacaagg agtttgagca gctggccccc gtgctggatg gtttcagcct      780
catgacctac gactactcta cagcgcacat gcctggccct aatgcacccc tgtcctgggt      840
tcgagcctgc gtccagggtcc tggacccgaa gtccaagtgg cgaagcaaaa tctcctggg      900
gctcaacttc tatggtatgg actacgcgac ctccaaggat gcccgtagag ctgttgctcg      960
ggccaggtac atccagacac tgaaggacca caggccccgg atggtgtggg acagccaggy      1020
ctcagagcac ttcttcgagt acaagaagag ccgcagtggg aggcacgtcg tcttctaccc      1080
aaccctgaag tccctgcagg tgcggctgga gctggccccg gagctgggag ttgggggtctc      1140
tatctgggag ctgggccagg gcctggacta cttctacgac ctgctctagg tgggcattgc      1200
ggcctccgag gtggacgtgt tcttttctaa gccatggagt gagtgagcag gtgtgaaata      1260
caggcctnca ctccgttcaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa      1320
aaaaaaaaact cgag                                     1334

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<210> 1230

<211> 1112

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1022)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1079)

<223> n equals a,t,g, or c

<400> 1230

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ggcgttttcc ggccgtgcgt ttgtggccgt ccggcctccc tgacatgcag ccctctggac      60
cccgaggttg gaccctactg tgacacacct accatgcgga cactcttcaa cctcctctgg      120

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cttgccctgg cctgcagccc tgttcacact accctgtcaa agtcagatgc caaaaaagcc      180
gcctcaaaga cgctgctgga gaagagtcag ttttcagata agccgggtgca agaccgggggt      240
ttgggtggtga cggacctcaa agctgagagt gtggttcttg agcatcgag ctactgctcg      300
gcaaaggccc gggacagaca ctttgctggg gatgtactgg gctatgtcac tccatggaac      360
agccatggct acgatgtcac caaggtcttt gggagcaagt tcacacagat ctcacccgtc      420
tggctgcagc tgaagagacg tggccgtgag atgtttgagg tcacgggcct ccacgacgtg      480
gaccaagggt ggatgcgagc tgtcaggaag catgccaaagg gcctgcacat agtgcctcgg      540
ctcctgtttg aggactggac ttacgatgat ttccggaacg tcttagacag tgaggatgag      600
atagaggagc tgagcaagac cgtggtccag gtggcaaaga accagcattt cgatggcttc      660
gtggtggagg tctggaacca gctgctaagc cagaagcgcg tgggcctcat ccacatgctc      720
accacttgg ccgaggtctt gcaccaggcc cggtgctgg ccctcctggt catcccgctt      780
gccatcacc ccgggaccga ccagctgggc atgttcacgc acaaggagtt tgagcagctg      840
gccccctgct tggatggttt cagcctcatg acctacgact actctacagc gcacagcct      900
ggccctaata caccctgtc ctgggttcga gcctgcgtcc aggtcctgga cccgaartyc      960
aagtggcgaa caaaatcctc ctggggstca acttctatgg watggactam gcgacytcca     1020
anggatgccc gtkarcctgt tgtcggggsc aggtamatyc agamactgaa rgaccacang     1080
ccccggatgg tgttggacag caagcctcaa ag                                     1112

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<210> 1231

<211> 2474

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2316)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2382)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2447)

<223> n equals a,t,g, or c

<400> 1231

ataagagaca gcgtcagggg ggcggagcct atggaaaaac gccagcaacg cggnccttttt	60
acggttcctg gccttttgcg ggccttttgc tcacatgttc tttcctgcgt tatccccctga	120
ttctgtggat aaccgtatta ccgcctttga gtgagctgat accgctcgcc gcagccgaac	180
gaccgagcgc agcgagtcag tgagcgagga agcggaagag cgcccaatac gcaaaccgcc	240
tctccccgcg cggtggccga ttcattaatg cagctggcac gacaggtttc ccgactggaa	300
agcgggcagt gacgcgaacg caattaatgt gagttagctc actcattagg caccacaggc	360
tttacacttt atgcttcagg ctctgtatgt gtgtggaatt gtgagcggat aacaatttca	420
cacaggaaac agctatgacc atgattacgc caagctcgaa attaaccctc actaaagggg	480
acaaaagctg gagctccacc gcgggtggcgg ccgctctaga actagtggat cccccgggct	540
gcaggaattc ggcacgaggt ccggcctccc tgacatgcag atttccaccc agaagacaga	600
gaaggagcca gtggtcatgg aatgggctgg ggtcaaagac tgggtgcctg ggagctgagg	660
cagccacgtt ttcagcctgg ccagccctct ggaccccgag gttggaccct actgtgacac	720
acctaccatg cggacactct tcaacctcct ctggcttgcc ctggcctgca gccctgttca	780
cactaccctg tcaaagtcag atgccaaaaa agccgcctca aagacgctgc tggagaagag	840
tcagttttca gataagccgg tgcaagaccg gggtttgggtg gtgacggacc tcaaagctga	900
gagtgtggtt cttgagcatc gcagctactg ctcggaagag gcccgggaca gacactttgc	960
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ctttgggagc aagttcacac agatctcacc cgtctggctg cagctgaaga gacgtggccg	1080
tgagatgttt gaggtcacgg gcctccacga cgtggaccaa ggggtggatgc gagctgtcag	1140
gaagcatgcc aagggcctgc acatagtgcc tcggctcctg tttgaggact ggacttacga	1200
tgatttccgg aacgtcttag acagtgagga tgagatagag gagctgagca agaccgtggt	1260
ccaggtggca aagaaccagc atttcgatgg ctctgtgggt gaggtctgga accagctgct	1320
aagccagaag cgcgtgggccc tcatccacat gctcaccac ttggccgagg ctctgcacca	1380
ggcccggtg ctggccctcc tgggtcatccc gcctgccatc acccccgga ccgaccagct	1440
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catgacctac gactactcta cagcgcatca gcctggccct aatgcacccc tgtcctgggt	1560
tcgagcctgc gtccaggtcc tggacccgaa gtccaagtgg cgaagcaaaa tcctcctggg	1620

gctcaacttc tatggtacat ccagacactg aaggaccaca ggccccggat ggtgtgggac 1680
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 gtgaaataca ggccctccact ccgttaaaaa aaaaaaaaaa aaaaaaaact cgagggggggg 1980
 cccggtaccc aattcgccct atagtgagtc gtattacaat tctactggccg tcgttttaca 2040
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 tttcgccagc tggcgtaata gcgaagaggc ccgcaccgat cgcccttccc aacagttgcg 2160
 cagcctgaat ggcgatggc aaattgtaag cgtaatatatt ttgttaaaat tcgcgtaaa 2220
 tttttgttaa atcagctcat tttttaacca ataggccgaa atcggcaaaa tcccttataa 2280
 atcaaaagaa tagaccgaga taggggtgag tggtgntcca gtttgaaca agagtccact 2340
 attaaagaac gtggactcca acgtcaaagg gcgaaaaacc gnctatcagg gcgatggccc 2400
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 ttaatcgga accc 2474

<210> 1232

<211> 307

<212> PRT

<213> Homo sapiens

<400> 1232

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro
 1 5 10 15
 Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys
 20 25 30
 Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg
 35 40 45
 Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His
 50 55 60
 Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp
 65 70 75 80
 Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr
 85 90 95
 Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln

610

100	105	110
Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp		
115	120	125
Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu		
130	135	140
His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe		
145	150	155 160
Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr		
165	170	175
Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu		
180	185	190
Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met		
195	200	205
Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu		
210	215	220
Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met		
225	230	235 240
Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe		
245	250	255
Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn		
260	265	270
Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys		
275	280	285
Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Thr		
290	295	300
Ser Arg His		
305		

<210> 1233

<211> 363

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (307)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1233

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro
1 5 10 15

Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys
20 25 30

611

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg
 35 40 45
 Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His
 50 55 60
 Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp
 65 70 75 80
 Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr
 85 90 95
 Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln
 100 105 110
 Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp
 115 120 125
 Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu
 130 135 140
 His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe
 145 150 155 160
 Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr
 165 170 175
 Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu
 180 185 190
 Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Thr Asp Gln Leu Gly
 195 200 205
 Met Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly
 210 215 220
 Phe Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro
 225 230 235 240
 Asn Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro
 245 250 255
 Lys Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly
 260 265 270
 Met Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala
 275 280 285
 Arg Tyr Ile Gln Thr Leu Lys Asp His Arg Pro Arg Met Val Trp Asp
 290 295 300
 Ser Gln Xaa Ser Glu His Phe Phe Glu Tyr Lys Lys Ser Arg Ser Gly
 305 310 315 320
 Arg His Val Val Phe Tyr Pro Thr Leu Lys Ser Leu Gln Val Arg Leu
 325 330 335

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613

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 Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His
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 Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp
 65 70 75 80
 Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr
 85 90 95
 Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln
 100 105 110
 Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp
 115 120 125
 Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu
 130 135 140
 His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe
 145 150 155 160
 Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr
 165 170 175
 Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu
 180 185 190
 Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met
 195 200 205
 Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu
 210 215 220
 Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met
 225 230 235 240
 Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe
 245 250 255
 Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn
 260 265 270
 Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys
 275 280 285
 Xaa Lys Trp Arg Thr Lys Ser Ser Trp Gly Ser Thr Ser Met Xaa Trp
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614

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<212> PRT

<213> Homo sapiens

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 35 40 45

Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His
 50 55 60

Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp
 65 70 75 80

Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr
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Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln
 100 105 110

Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp
 115 120 125

Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu
 130 135 140

His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe
 145 150 155 160

Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr
 165 170 175

Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu
 180 185 190

Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met
 195 200 205

Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu
 210 215 220

Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met
 225 230 235 240

Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe
 245 250 255

Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn
 260 265 270

615

Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys
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Ser Arg His
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 35 40 45

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Leu Lys Cys Gln Val Lys Asp His Glu Asp Ser Ser Leu Gln Trp Ser
 85 90 95

Asn Pro Ala Gln Gln Thr Leu Tyr Phe Gly Glu Lys Arg Ala Leu Arg
 100 105 110

Asp Asn Arg Ile Gln Leu Val Thr Ser Thr Pro His Glu Leu Ser Ile
 115 120 125

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 130 135 140

Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu Val Thr Val Leu
 145 150 155 160

616

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 Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser Gly Ser Lys Pro
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 Ala Ala Arg Leu Thr Trp Arg Lys Gly Asp Gln Glu Leu His Gly Glu
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 Pro Thr Arg Ile Gln Glu Asp Pro Asn Gly Lys Thr Phe Thr Val Ser
 210 215 220
 Ser Ser Val Thr Phe Gln Val Thr Arg Glu Asp Asp Gly Ala Ser Ile
 225 230 235 240
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 245 250 255
 Ser Gln Arg Ile Glu Val Leu Tyr Thr Pro Thr Ala Met Ile Arg Pro
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 305 310 315 320
 Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly Cys Thr Ala Thr Ser
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<213> Homo sapiens

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 35 40 45
 Thr Val Val Ala Gly Gly Thr Val Val Leu Lys Cys Gln Val Lys Asp
 50 55 60

617

His Glu Asp Ser Ser Leu Gln Trp Ser Asn Pro Ala Gln Gln Thr Leu
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 Tyr Phe Gly Glu Lys Arg Ala Leu Arg Asp Asn Arg Ile Gln Leu Val
 85 90 95
 Thr Ser Thr Pro His Glu Leu Ser Ile Ser Ile Ser Asn Val Ala Leu
 100 105 110
 Ala Asp Glu Gly Glu Tyr Thr Cys Ser Ile Phe Thr Met Pro Val Arg
 115 120 125
 Thr Ala Lys Ser Leu Val Thr Val Leu Gly Ile Pro Gln Lys Pro Ile
 130 135 140
 Ile Thr Gly Tyr Lys Ser Ser Leu Arg Glu Lys Asp Thr Ala Thr Leu
 145 150 155 160
 Asn Cys Gln Ser Ser Gly Ser Lys Pro Ala Ala Arg Leu Thr Trp Arg
 165 170 175
 Lys Gly Asp Gln Glu Leu His Gly Glu Pro Thr Arg Ile Gln Glu Asp
 180 185 190
 Pro Asn Gly Lys Thr Phe Thr Val Ser Ser Ser Val Thr Phe Gln Val
 195 200 205
 Thr Arg Glu Asp Asp Gly Ala Ser Ile Val Cys Ser Val Asn His Glu
 210 215 220
 Ser Leu Lys Gly Ala Asp Arg Ser Thr Ser Gln Arg Ile Glu Val Leu
 225 230 235 240
 Tyr Thr Pro Thr Ala Met Ile Arg Pro Asp Pro Pro His Pro Arg Glu
 245 250 255
 Gly Gln Lys Leu Leu Leu His Cys Glu Gly Arg Gly Asn Pro Val Pro
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<212> PRT

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<211> 34

<212> PRT

<213> Homo sapiens

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<211> 42

<212> PRT

<213> Homo sapiens

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Asp Met Leu Ala Ser Gln Asp Ser Gln Pro
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<210> 1242

<211> 8

<212> PRT

<213> Homo sapiens

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<210> 1243

<211> 63

619

<212> PRT

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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tcagcatcag	catcagcaat	gtggccctgg	cagacgaggg	cgagtacacc	tgctcaatct	480
tcactatgcc	tgtgcgaact	gccaagtccc	tcgtcactgt	gctaggaatt	ccacagaagc	540
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agtcttctgg	gagcaagcct	gcagcccggc	tcacctggag	aaaggggtgac	caagaactcc	660
acggagaacc	aaccgcgata	caggaagatc	ccaatggtaa	aaccttcact	gtcagcagct	720
cggtgacatt	ccagggttacc	cgggaggatg	atggggcgag	catcgtgtgc	tctgtgaacc	780
atgaatctct	aaagggagct	gacagatcca	cctctcaacg	cattgaagtt	ttatacacac	840
caactgcgat	gattaggeca	gaccctcccc	atcctcgtga	gggccagaag	ctgttgctac	900

620

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Tyr Leu Pro Arg Leu Tyr Leu Asp Ile His Asn Tyr Cys Val Leu Asp
      35              40              45

ys Leu Arg Asp Phe Val Ala Ser Pro Pro Cys Trp Lys Val Ala Gln
      50              55              60

Val Asp Ser Leu Lys Asp Lys Ala Arg Lys Leu Tyr Thr Ile Met Asn
      65              70              75              80

Ser Phe Cys Arg Arg Asp Leu Val Phe Leu Leu Asp Asp Cys Asn Ala
      85              90              95

Leu Glu Tyr Pro Ile Pro Val Thr Thr Val Leu Pro Asp Arg Gln Arg
      100              105              110

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 253, line 12.

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit
February 16, 2001

Accession Number
PTA-3070

C. ADDITIONAL INDICATIONS (leave blank if not applicable)

This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

	For receiving Office use only			For International Bureau use only	
<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
			21 MAR 2001		
Authorized officer			Authorized officer		
			J. N. S. Adams.		

PCT/US01/05614
ATCC Deposit No. PTA-3070

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations)

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

PCT/US01/05614

ATCC Deposit No.: PTA-3070

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 August 2001 (30.08.2001)

PCT

(10) International Publication Number
WO 01/062891 A3

(51) International Patent Classification⁷: **C07H 21/04**,
21/02, C07K 5/00, 14/00, C12Q 1/68, C12N 15/63, 15/85,
15/86

(21) International Application Number: **PCT/US01/05614**

(22) International Filing Date: 21 February 2001 (21.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/184,836 24 February 2000 (24.02.2000) US
60/193,170 29 March 2000 (29.03.2000) US

(71) Applicant (for all designated States except US): **HUMAN
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5502 Manorfield Road, Rockville, MD 20853 (US). **EBNER, Reinhard** [DE/US]; 9906 Shelburne Terrace,
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W. [US/US]; 3142 Quesada Street, N.W., Washington,
DC 20015 (US). **MOORE, Paul, A.** [GB/US]; 19005
Leatherbark Drive, Germantown, MD 20874 (US).
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#24, Gaithersburg, MD 20878 (US). **ROSEN, Craig**,
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MD 20882 (US). **RUBEN, Steven, M.** [US/US]; 18528
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Daniel, R. [US/US]; 15050 Stillfield Place, Centreville,
MD 22020 (US). **YOUNG, Paul, E.** [US/US]; 122 Beck-
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MD 20878 (US). **FLORENCE, Kimberly, A.** [US/US];
12805 Atlantic Avenue, Rockville, MD 20851 (US). **WEI,**
Ying-Fei [CN/US]; 242 Gravatt Drive, Berkeley, CA
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Apt. 3034, Sunnyvale, CA 94086 (US). **KYAW, Hla**
[MM/US]; 520 Sugarbush Circle, Frederick, MD 21703
(US). **FISCHER, Carrie, L.** [US/US]; 5810 Hall Street,
Burke, VA 22015 (US). **FERRIE, Ann, M.** [US/US]; 120

Fox Run Drive, Tewksbury, MA 01876 (US). **FAN, Ping**
[CN/US]; 13 Lake Potomac Court, Potomac, MD 20854
(US). **FENG, Ping** [CN/US]; 4 Relda Court, Gaithersburg,
MD 20878 (US). **ENDRESS, Gregory, A.** [US/US];
408 Bridge Road, Florence, MA 01062 (US). **DILLON,**
Patrick, J. [US/US]; 1055 Snipe Court, Carlsbad, CA
92009 (US). **CARTER, Kenneth, C.** [US/US]; 11600
Brandy Hall Lane, North Potomac, MD 20878 (US).
BREWER, Laurie, A. [US/US]; 410 Van Dyke Street,
Apt. 115, St. Paul, MN 55119 (US). **YU, Guo-Liang**
[CN/US]; 242 Gravatt Drive, Berkeley, CA 94705 (US).
ZENG, Zhizhen [CN/US]; 410 Shipwrighter Way, Lans-
dale, PA 19446 (US). **GREENE, John, M.** [US/US]; 872
Diamond Drive, Gaithersburg, MD 20878 (US).

(74) Agents: **HOOVER, Kenley, K.** et al.; C/O Human
Genome Sciences, Inc., 9410 Key West Avenue, Rockville,
MD 20850 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
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- with (an) indication(s) in relation to deposited biological
material furnished under Rule 13bis separately from the
description

(88) Date of publication of the international search report:
17 July 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: 207 HUMAN SECRETED PROTEINS

(57) Abstract: The present invention relates to the novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for produc-
ing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating
diseases, disorders, and/or conditions related to these novel human secreted proteins.

WO 01/062891 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/05614

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.5, 24.3; 530/350, 300; 435/6; 69.1, 252.3; 320.1; 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/54963 A2 (HUMAN GENOME SCIENCES, INC.) 10 December 1998 (10.12.1998), polynucleotide, polypeptide, variants and fragments: see pages 192-199; vector, host cell, production of protein: see page 202-204; see all claims.	1-10, 14, 15, 21
X	Database: N_Geneseq_101002; Accession NO: AAV84411; BREWER et al.; "Human secreted protein gene 1 clone HLHDS67"; 01 March 1999; having 99.9% sequence identity to SEQ ID NO: 11; vector, host cell and ATCC deposit number: see page 2.	1-10, 14, 15, 21

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed.	

Date of the actual completion of the international search

30 APRIL 2003

Date of mailing of the international search report

16 MAY 2003

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/05614

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

CO7H 21/04; CO7H 21/02; CO7K 5/00; CO7K 14/00; C12Q 1/68; C12N 15/63; C12N 15/85, 15/86

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

536/23.1, 23.5, 24.3; 530/350, 300; 435/6; 69.1, 252.3; 320.1; 325

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

Database: GenEmbl_HTG, N_Geneseq_101002, Issued_Patents_NA, EST, Published_Applications_NA, A-Geneseq_101002, Issued_Patents_AA, PIR_73, SwissProt_40, SPTREMBL_21, Published_Applications_NA

EAST: USPAT, US-PGPUB, EPO, JPO, DERWENT

STN: BIOSIS, CAPLUS, EMBASE, MEDLINE, SCISEARCH

Search Terms: secreted proteins, polynucleotide, polypeptide, nucleic acid, melanocytes, neural crest derived cell, precerebellin, cerebellin, synaptic physiology/activity

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-238, claims 1-10, 14, 15 and 21, all in part, drawn to an isolated nucleic acid of SEQ ID NO X or a peptide of SEQ ID NO: Y, wherein X and Y are values that correlate to those listed in Table 1, and correspond to one of the cDNA Clone IDs, respectively. For examples,

If group 1 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein X is 11 and Y is 249.

If group 2 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein X is 12 and Y is 250.

Groups 239-476, claims 11, 12 and 16, all in part, each group directed to a peptide of SEQ ID NO: Y, wherein Y correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 239 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein Y is 249.

If group 240 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein Y is 250.

Groups 477-714, claim 13, in part, drawn to an isolated antibody which binds to a protein with SEQ ID NO Y, wherein Y correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 477 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein Y is 249.

If group 478 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein Y is 250.

Groups 715-952, claim 17, in part, drawn to a method for preventing, treating or ameliorating an undefined medical condition by administering a polypeptide of SEQ ID NO Y, wherein Y correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 715 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein Y is 249.

If group 716 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein Y is 250.

Groups 953-1190, claim 17, in part, drawn to a method for preventing, treating or ameliorating an undefined medical condition by administering a polynucleotide of SEQ ID NO X encoding a protein of SEQ ID NO Y, wherein X and Y correlate to one of those listed in Table 1, and correspond to one of the cDNA Clone IDs, respectively. For examples,

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-23 all in part
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-10, 14, 15 and 21, all in part; SEQ ID NO: 11, 249, 225, 463
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/05614

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database: A_Geneseq_101002; Accession NO: AAW88534; BREWER et al. "Secreted protein encoded by gene 1 clone HLHDS67;" 01 March 1999; having 99.3% sequence identity to SEQ ID NO: 249; vector, host cell and ATCC NO: see page 2.	1-10, 14, 15, 21
X	Database: N_Geneseq_101002; Accession NO: AAV84624; BREWER et al.; "Human secreted protein gene 45 clone HCESF40;" 01 March 1999; having 98.5% sequence identity to SEQ ID NO: 225; vector, host cell, ATCC NO: see page 3.	1-10, 14, 15, 21
X	Database: A_Geneseq_101002; Accession NO: AAW88747; BREWER et al. "Secreted protein encoded by gene 45 clone HCESF40;" having 99.5% sequence identity to SEQ ID NO: 463; vector, host cell and ATCC NO: see page 5.	1-10, 14, 15, 21
X	URADE et al. "Precerebellin is a cerebellum-specific protein with similarity to the globular domain of complement C1q B chain;" Proc. Natl. Acad. Sci. USA, Vol. 88, pp1069-1073, February 1991; cDNA encoding cerebellin sequence and vector : see, page 1069, col 2, third paragraph and under 'Materials and Methods.	1-6, 14, 15, 21
X	Database: PIR_73; Accession NO: A37873; URADE et al. "Cerebellin precursor-human;" 30 April 1991, having 52.3% sequence identity to SEQ ID NO: 463; see entire document.	1-7, 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/05814

If group 953 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein X is 11 and Y is 249.

If group 954 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein X is 12 and Y is 250.

Groups 1191-1428, claim 18, in part, drawn to a method of diagnosis of an undefined pathological condition by determining the presence or absence of a mutation in a polynucleotide of SEQ ID NO X, wherein X correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 1191 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein X is 11.

If group 1192 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein X is 12.

Groups 1429-1666, claim 19, in part, drawn to a method of diagnosis of an undefined pathological condition by determining the presence or amount of expression of the polypeptide of SEQ ID NO y, wherein y correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 1429 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein y is 249.

If group 1430 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein y is 250.

Groups 1667-1904, claim 20, in part, drawn to a method of identifying a binding partner to a polypeptide defined by SEQ ID NO Y, wherein Y correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 1667 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein Y is 249.

If group 1668 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein Y is 250.

Groups 1905-2142, claim 22, in part, drawn to a method of identifying an activity in a biological assay by identification of the protein in the supernatant wherein the cell expresses a polypeptide encoded by SEQ ID NO X, wherein X correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 1905 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein X is 11.

If group 1906 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ58, wherein X is 250.

Groups 2143-2380, claim 23, in part, each group directed to a peptide produced by the method for the identifying a binding partner to a polypeptide defined by SEQ ID NO: Y, wherein Y correlates to one of those listed in Table 1, and corresponds to one of the cDNA Clone IDs, respectively. For examples,

If group 2143 is elected, this correlates to Gene No 1, cDNA clone ID HLHDS67 of Table 1, wherein Y is 249.

If group 2144 is elected, this correlates to Gene No 2, cDNA clone ID HLHDZ67, wherein Y is 250.

The inventions listed as Groups 1-2380 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The polynucleotides and polypeptides of each of the clones in Table 1 are unrelated, each to the other. The polynucleotide sequences encode structurally distinct polypeptides and do not share a special technical feature. Furthermore, the technical feature that links the DNA, protein, antibody, methods of CDNA clone HLHDS67 (see Table 1) is not a contribution over the prior art. See the various documents cited in the search report. Thus the technical feature of the polynucleotide sequence is not special and the groups are not so linked under PCT Rule 13.1. Additionally the claimed methods produce different products and/or different results which are not coextensive and which do not share the same technical feature.